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Central Association of Obstetricians and Gynecologists,  
New Orleans, La., Oct. 4-6, 1956*

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# AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

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HOWARD C. TAYLOR, JR.

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## IN THE TREATMENT OF TOXEMIA OF PREGNANCY,

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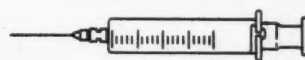


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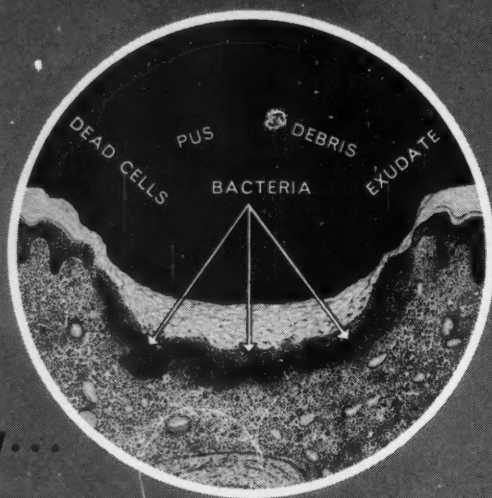
**References:** 1. Gamble, J.R., et al. Arch. Int. Med. 95:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. 42:805, 1953.



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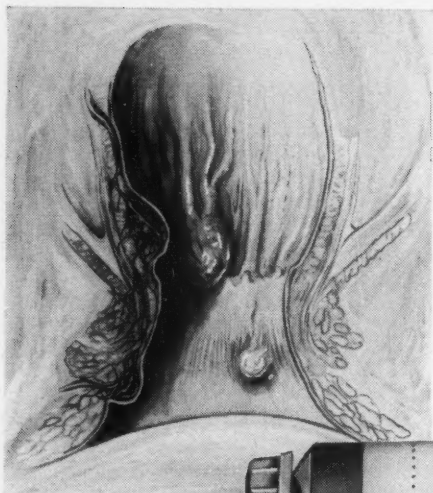
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3. Adriani, J.: Pharmacology of Anesthetic Drugs, Ed. 1941

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*References:* 1. Greenblatt, R. B.: *Obst. & Gynec.* 2:530, 1953. 2. Dill, L. V.: *M. Ann. District of Columbia* 23:667, 1954. 3. Greenblatt, R. B.: *Ann. New York Acad. Sc.* 61:713, 1955. 4. Javert, C. T.: *Obst. & Gynec.* 3:420, 1954. 5. Javert, C. T.: *Ann. New York Acad. Sc.* 61:700, 1955. 6. Barishaw, S. B.: *Exp. Med. & Surg.* 7:358, 1949. 7. Selsman, G. J. V., and Horoschak, S.: *Am. J. Digest. Dis.* 17:92, 1950.

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1. Crunden, A. B., Jr., and Davis, W. A.: *Am. J. Obst. & Gynec.* 65:311, 1953.
2. Bradley, J. E., et al.: *J. Pediat.* 38:41, 1951.
3. Tebrock, H. E., and Fisher, M. M.: *M. Times* 82:271, 1954.



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1. Spiesman, M. G. and Malow, L.: Amer. J. Proctology, June 1956.





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**References:** (1) Perl, G.; Guttmacher, A. F., and Raggazoni, H.: Male and Female Trichomoniasis — Diagnosis and Oral Treatment, *Obst. & Gynec.* 7:128, 1956. (2) Plentl, A. A.; Gray, M. J.; Neslen, E. D., and Dalali, S. J.: The Clinical Evaluation of 2-Acetylamino-5-Nitrothiazole, An Orally Effective Trichomonacide, *Am. J. Obst. & Gynec.* 71:116, 1956. (3) Perl, G.: Personal communication.







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1. Seegar, J.K.B.E., and Devlin, A.J.: Maryland M.J. 5:330 (June) 1956.

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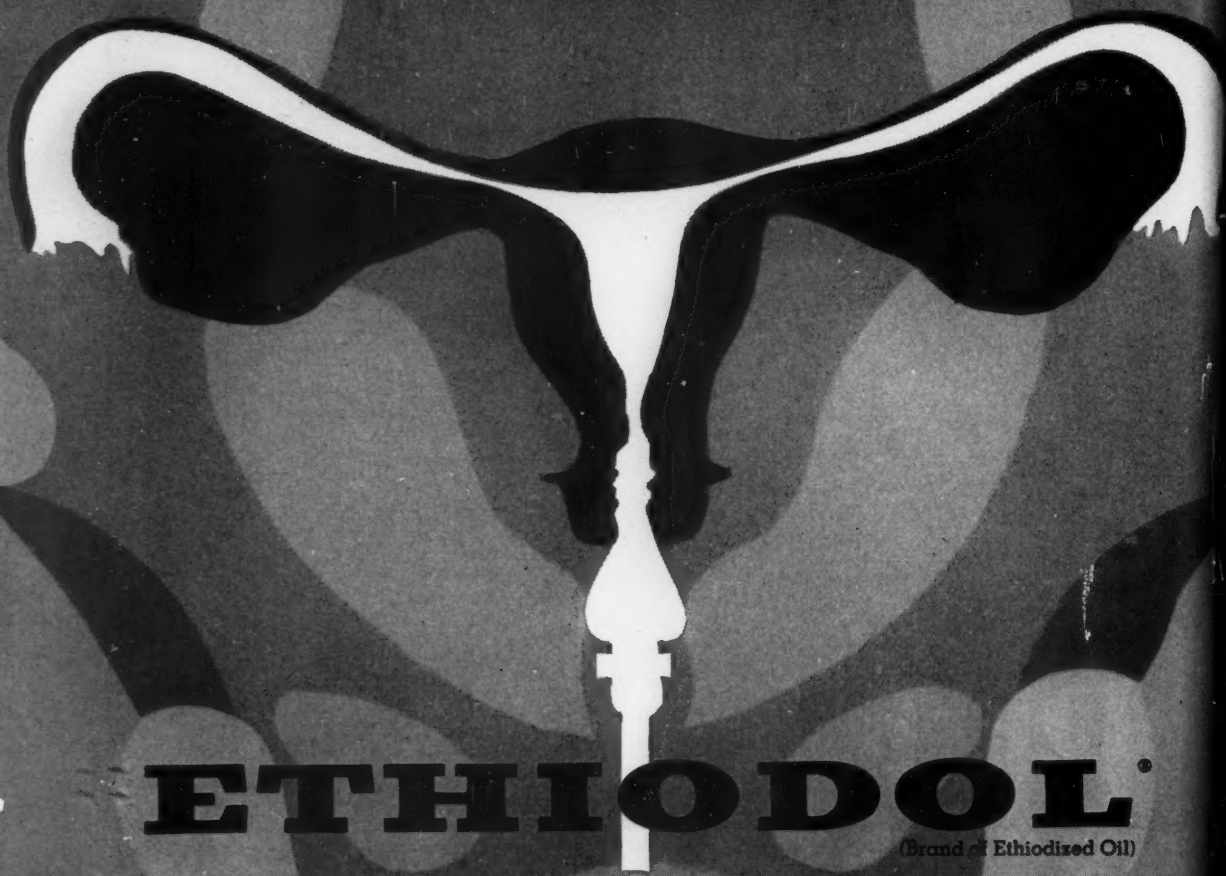


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REFERENCES

1. Canario, E. M., et al.: Am. J. Obst. & Gynec. 65:1298, 1953.
2. Gitman, L., and Koplowitz, A.: N. Y. St. J. Med. 50:2823, 1950.
3. Karnaky, K. J.: South. M. J. 45:1166, 1952.
4. Peña, E. F.: Med. Times 82:921, 1954; Am. J. Surg. 87:95, 1954.
5. Ross, J. W.: J. Nat. M. A. 43:20, 1951; 45:223, 1953.

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1. Bacala, J.C.: The Use of the Systemic Hemostat,  
Carbazochrome Salicylate, West. J. Surg. 64:88 (Jan., 1956)

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Peele, J.C.: Adrenosem in the Control of Hemorrhage from the Nose and Throat, *A.M.A. Arch. of Otolaryng.* 61:450 (April, 1955)

"Our experience of the effect of carbazochrome salicylate on 317 surgical indications and 13 obstetrico-gynecological conditions has been therapeutically encouraging and successful for the control of capillary bleeding."

Bacala, J.C.: The Use of the Systemic Hemostat Carbazochrome Salicylate, *West. J. Surg.* 64:88 (Jan., 1956)

"We have also noticed that bleeding stopped more promptly on the operating table."

Owings, Capers B.: The Control of Postoperative Bleeding with Adrenosem, *Laryngoscope* 55:21 (Jan., 1955)

"*Primary* hemorrhage occurred in 1.7 percent and *secondary* hemorrhage in 1 percent of the 300 control patients, but in *none* of the 500 children who received preoperative and postoperative medication [Adrenosem Salicylate]."

Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, *N.Y. State J. Med.* 55:886 (Mar., 1956)

"Adrenosem Salicylate is nontoxic and has a high index of therapeutic safety. At the recommended dosage levels there are no contraindications. It has no cumulative effect. Patients treated for more than two years show no toxic effects attributable to the drug."

Riddle, A.C., Jr.: Adrenosem Salicylate: A Systemic Hemostat, *Oral Surg., Oral Med., Oral Path.* 6:617 (June, 1955)

Adrenosem Salicylate is supplied in

- ampuls
- tablets
- and as a syrup.

Write for comprehensive illustrated brochure describing the action and uses of Adrenosem Salicylate.

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*new*

*a new measure in therapy  
of overweight*

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(brand of phenmetrazine hydrochloride)

**...reduces risk in reducing**

A totally new development in anorexigenic therapy, PRELUDIN substantially reduces the risks and discomfort in reducing.

**Distinctive in its Chemistry:** PRELUDIN is a totally new compound of the oxazine series.

**Distinctive in Effectiveness:** In three years of clinical trials PRELUDIN has consistently demonstrated outstanding ability to produce significant and progressive weight loss through voluntary effortless restriction of caloric intake.

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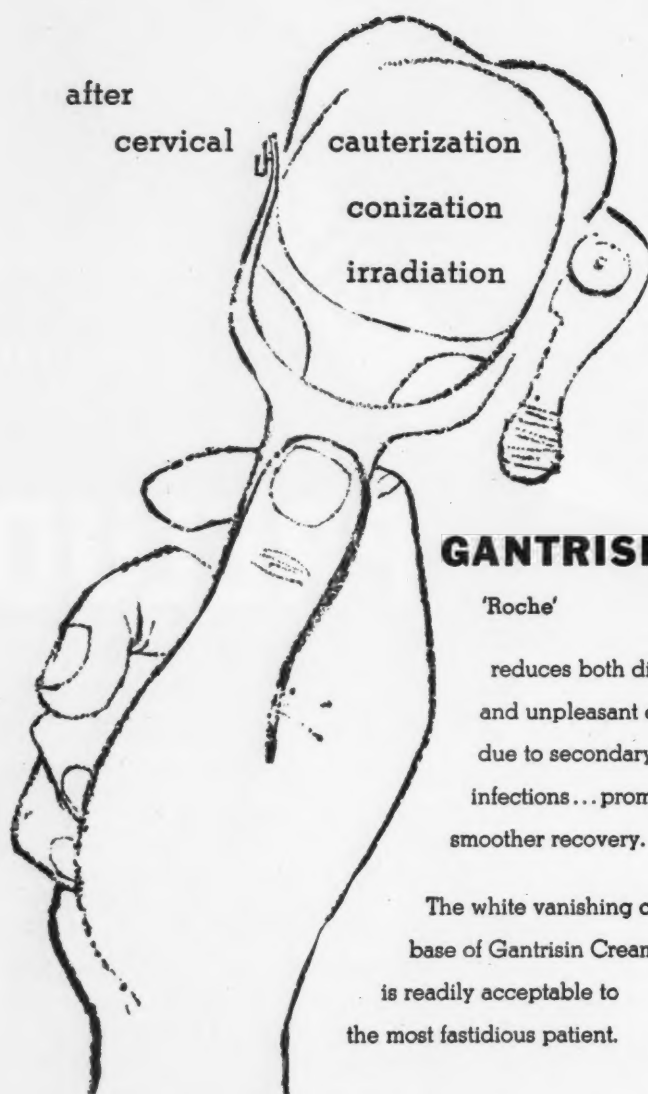
**For your patient's greater comfort:** PRELUDIN curtails appetite without destroying enjoyment of meals...causes a mild evenly sustained elevation of mood that keeps the patient in an optimistic and cooperative frame of mind.

**Recommended Dosage:** One tablet two or three times daily taken one hour before meals. Occasionally smaller dosage suffices.

PRELUDIN<sup>®</sup> (brand of phenmetrazine hydrochloride). Scored, square, pink tablets of 25 mg.  
Under license from C. H. Boehringer Sohn, Ingelheim.

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## GANTRISIN CREAM

'Roche'

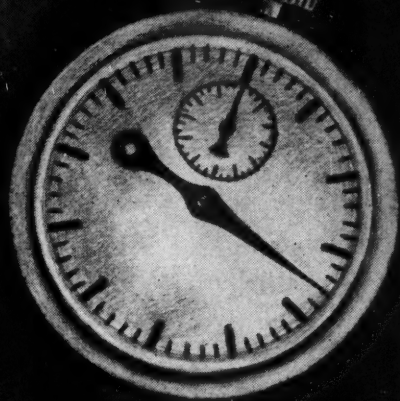
reduces both discharge  
and unpleasant odors  
due to secondary  
infections... promotes  
smoother recovery.

The white vanishing cream  
base of Gantrisin Cream  
is readily acceptable to  
the most fastidious patient.



Gantrisin® — brand of sulfisoxazole





the critical  
fibrinogen  
index in  
60  
seconds



Ortho Pharmaceutical Corporation  
RARITAN, NEW JERSEY



# Local Estrogen Therapy Controls Juvenile Vaginitis

*Also simplifies treatment of senile vaginitis  
and favors rapid healing in vaginal surgery*

Disappearance of causative organisms and a "favorable response and cure" of vaginitis or vulvitis occurred in all patients treated with "Premarin" Vaginal Cream (age range, 1½ to 10 years). This was attributed to the development of a postpuberal vaginal epithelium with an acid pH range unfavorable for the growth of pathogenic organisms. There was no recurrence of infection after treatment was stopped, and vaginal epithelium, pH, and flora gradually returned to the prepuberal state.<sup>1</sup>



## "Premarin"<sup>®</sup> Vaginal Cream

... in a nonliquefying base, is standardized in terms of the weight of active, water-soluble estrogen content expressed as sodium estrone sulfate (0.625 mg. per gram). Presented in combination package No. 874—1½ oz. tube with specially designed calibrated applicator; also refill available.

Average suggested dosage: 2 to 4 Gm. daily.

**In senile vaginitis**, "Premarin" Vaginal Cream regenerates the atrophic mucosa by promoting proliferation and vascularity of the epithelium. Treatment provides an "... almost immediate healing and soothing effect."<sup>2</sup>

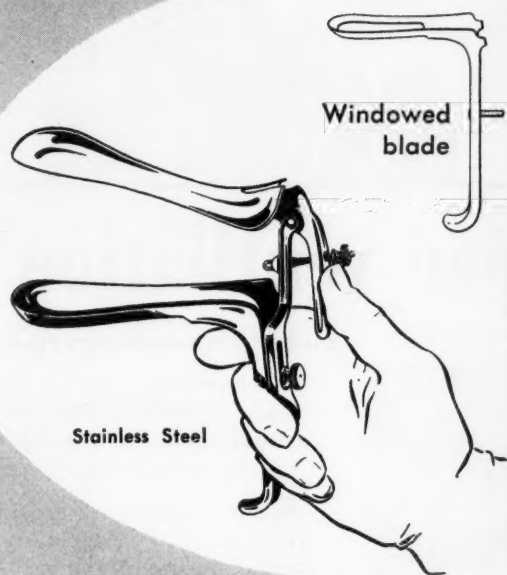
**Pre- and postoperatively in the postmenopausal patient**, local application of "Premarin" Vaginal Cream before and after surgery tends to restore the atrophic and friable mucosa to a more normal state, thus facilitating the surgical procedure and promoting more rapid healing.<sup>3,4</sup>

*Bibliography on request.*



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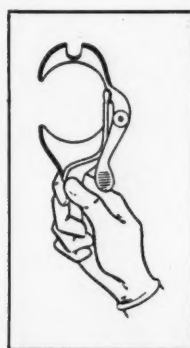
## Introducing the all-new Lawton WEISMAN-GRAVES VAGINAL SPECULUM...

Now available with right  
or left lateral opening and  
windowed lower blade

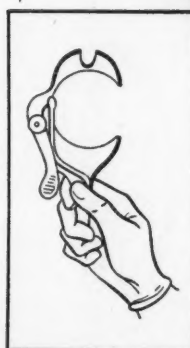
This versatile instrument features a number of basic, long-needed improvements, and may replace the old style specula for most diagnostic and operative procedures.

- Single-arm construction, with either right or left side open.
- Permits greater freedom of action in manipulation of instruments, such as canula, tenaculum, biopsy, or dressing forceps. Provides enlarged field of vision.
- Speculum may be removed easily while other instruments are left in situ. This is particularly helpful during hysterosalpingography and pneumoperitoneum.
- Windowed lower blade affords better visualization of vagina. Washing, powdering, medical treatment, and minor surgery may be performed directly through blade opening.

PRICE: With solid blades \$8.00  
With windowed blade \$9.50  
For medium size



Left  
lateral opening



Right  
lateral opening



THE *Lawton* COMPANY

425 FOURTH AVENUE, NEW YORK 16, N. Y.

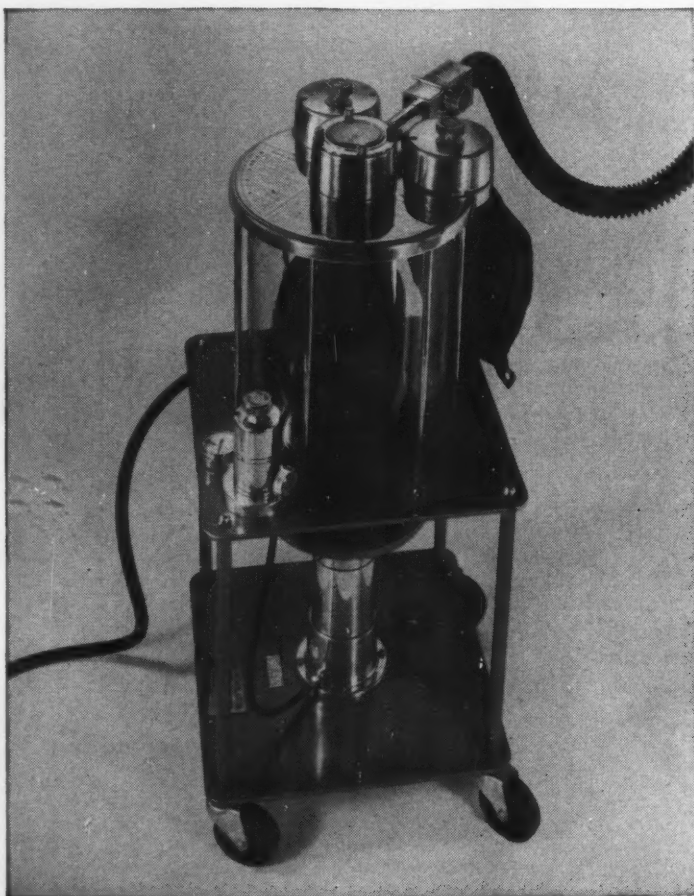
Write for free illustrated circular on  
LAWTON Gynecological Specialties



during  
general  
anesthesia



## to insure proper ventilation



Three-quarters of the U.S. medical schools now have JEFFERSON VENTILATORS in use in one or more affiliated hospitals.

### THE JEFFERSON VENTILATOR

1. *Automatically* exerts rhythmic, negative-positive pressure for adequate pulmonary ventilation, without circulatory depression;
2. *Helps avoid respiratory acidosis*, maintain proper arterial oxygen-carbon dioxide saturation;
3. *Frees anesthesiologist* for administration of fluids, checking blood pressure, and other vital tasks.

THE JEFFERSON VENTILATOR is a clinically proved, fully automatic, portable device • Pneumatically activated (by air or oxygen, without electrical hazard) • Developed in cooperation with *Jefferson Medical College* • Connects to any closed or semi-closed-circuit anesthesia apparatus • Accommodates automatically to the requirements of the patient • Rebreathing bag may be manually operated • Independent controls for phase, positive pressure, negative pressure, respiration rate • Automatic "overflow" valve prevents over-distention of rebreathing bag • For orders, information, phone collect: Hatboro, Pa. OSborne 5-5200.

# THE Jefferson Ventilator

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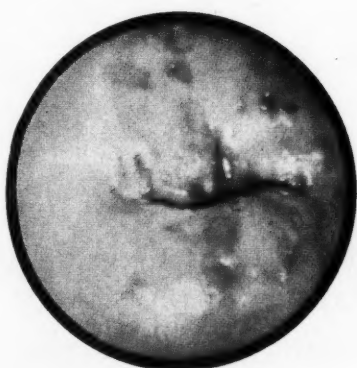
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Hatboro, Pa.

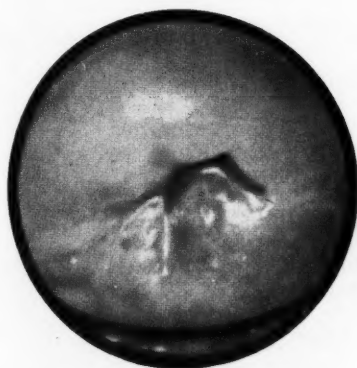




Pre-cauterization



2 weeks post-cauterization



3 weeks post-cauterization,  
healing nearly complete

PHOTOGRAPHS BY SCHWARTZ, J.: AM. J. OBST. 63:579, 1952.



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## FASTER HEALING, GREATER PATIENT COMFORT

Whether cauterization, conization, other surgical operation or radiation of the cervix uteri is indicated, **FURACIN Vaginal Suppositories** can aid materially. Administered before and after these procedures, they eliminate infection; minimize discharge, malodor and irritation; facilitate healing and provide a more rapid and comfortable convalescence. In conjunction with radiotherapy, they control infection and thus contribute to "a better response of the malignant tissue to a given unit of radiation."\* **FURACIN Vaginal Suppositories** do not cause monilial superinfection and are safe for prolonged use.

**FORMULA:** 0.2% **FURACIN** in water-miscible base; hermetically sealed in yellow foil.

\*Schwartz, J., and Nardiello, V.: Am. J. Obst. 65:1069, 1953.

### **FURACIN® VAGINAL**

BRAND OF NITROFURAZONE

SUPPOSITORIES

ALSO AVAILABLE: **FURACIN URETHRAL SUPPOSITORIES**



**NITROFURANS**

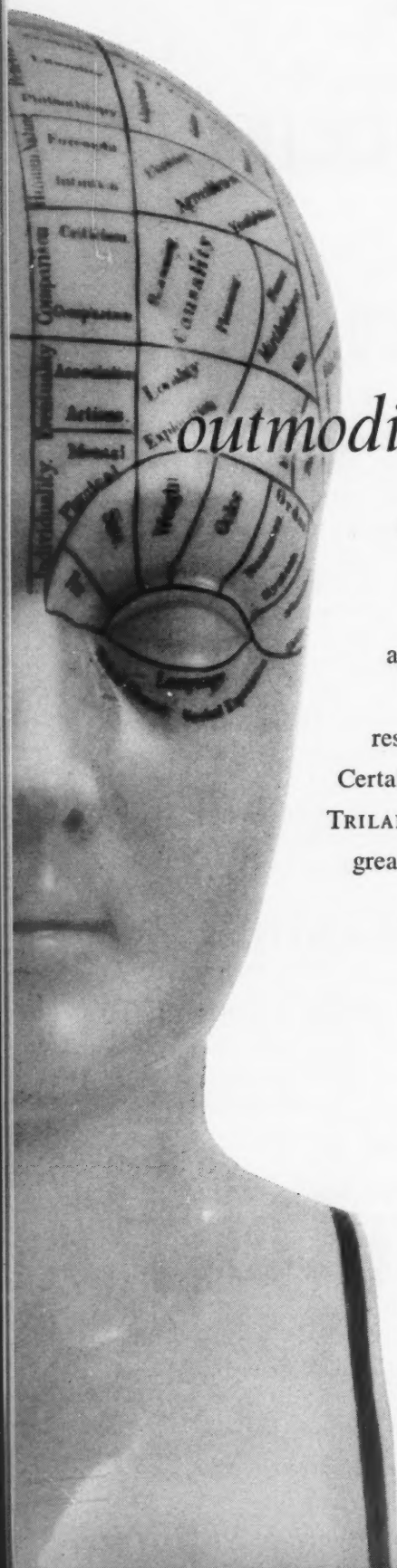
a new class of antimicrobials—neither antibiotics nor sulfonamides

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NORWICH, NEW YORK

A N N O U N C I N G . . . T H E F U L L



## *outmoding older concepts*

IN THE FULL RANGE OF AGITATED MENTAL  
AND EMOTIONAL DISTURBANCES FROM SEVERE  
PSYCHOSES TO ANXIETY AND TENSION STATES,  
age-old methods of merely sedating the anxious or of  
managing hospitalized patients by heavy sedation or physical  
restraints have been largely supplanted by the older tranquilizers.  
Certain of the latter agents in turn are due to be superseded by  
TRILAFON, a new all-purpose tranquilizing agent which offers  
greater potency combined with increased flexibility and an adequate  
margin of safety in the recommended dosage ranges.

L A N G E T R A N Q U I L I Z E R

*with markedly enhanced potency*

**Trilafon\***  
NEW (pronounced Tril'-a-fon) perphenazine

*equally valuable in all degrees of psychic  
disorder responsive to tranquilizing therapy*

AGITATED HOSPITALIZED PSYCHOTICS

AMBULATORY PSYCHONEUROTICS

ANXIETY AND TENSION STATES

- *potency increased 5-fold over chlorpromazine*
- *uniquely high therapeutic index—10 times higher than chlorpromazine in animal studies*
- *jaundice notably infrequent in studies to date*
- *significant hypotension virtually absent*
- *no agranulocytosis reported*
- *skin photosensitivity neither observed nor elicited experimentally*
- *nasal congestion uncommon*
- *mild insomnia and motor restlessness infrequent*

*unexcelled also as a potent antiemetic*

*Dosage:* For specific information consult Schering literature.

*Packaging:* TRILAFON Tablets: 2, 4, and 8 mg., bottles of 50 and 500; 16 mg. (for hospital use), bottle of 500.

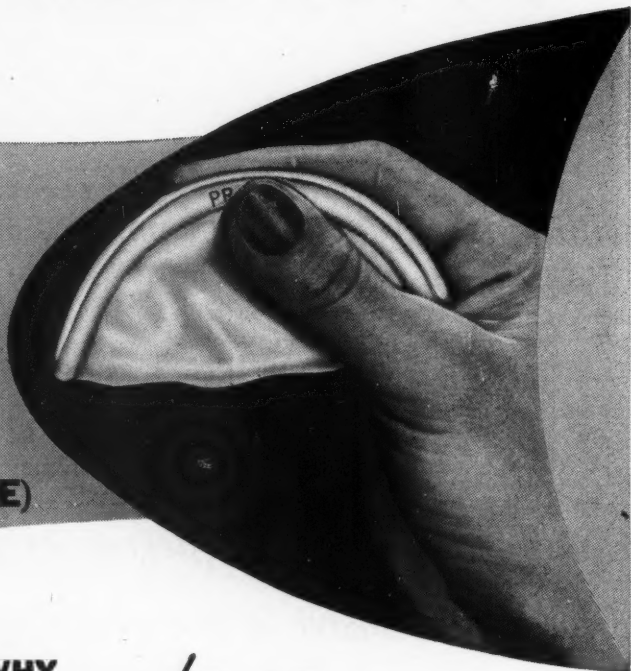
*Schering*  
\*T.M. TR-J-337



# WORTH YOUR INVESTIGATION

**Koro-Flex**  
TRADE MARK

*improved*  
**THE DIAPHRAGM  
WITH THE  
CONTOURING  
SPRING (ARCING TYPE)**



## SIX REASONS WHY PHYSICIANS ARE RECOMMENDING *Koro-Flex*



FIG. 1

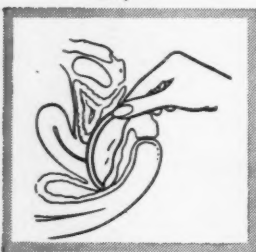


FIG. 2

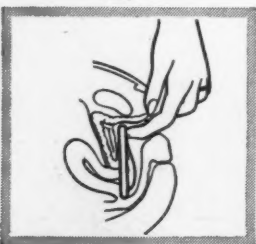


FIG. 3

1. Expressly designed to assure your patient ease of insertion and automatic placement.
2. Conserves physician's time by reducing fitting and instruction period.
3. Patients learn faster and develop greater confidence because of the ease with which they learn to place and use the diaphragm.
4. Affords greater patient protection by locking in spermicidal lubricant and delivering it directly under and next to the os uteri.
5. Folds behind pubic bone with suction-like action forming a more effective barrier.
6. Simple to remove.

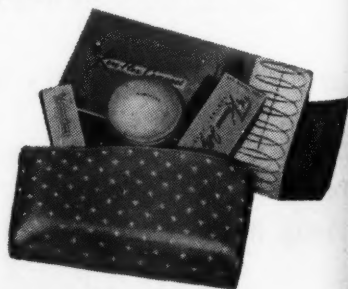
When compressed, diaphragm forms into semi-curve or half-moon shape (Fig. 1) permitting it to pass easily along floor of the vagina beyond cervix (Fig. 2) without any difficulty. No mechanical inserter or introducer required (see Fig. 2) since the KORO-FLEX will not buckle or butterfly in form.

KORO-FLEX (contouring) Diaphragm is ideal, not only where ordinary coilspring diaphragms are indicated but for Flat rim (Mensinga) type as well.

May be used in cases of mild prolapse, cystocele or rectocele.

Suggest the convenient-economical  
KORO-FLEX COMPACT 60-95 mm  
Sanitary plastic bag with zipper closure.  
Diaphragm, tube KOROMEX Jelly (3 oz.),  
Cream (1 oz. trial size).

Available at all prescription pharmacies. Write for descriptive literature.



Holland-Rantos Co., Inc. Manufacturers of **KOROMEX** Products, New York 13, N. Y.



keep  
the "reducer"  
happy

# 'Methedrine'

brand Methamphetamine Hydrochloride

'Methedrine' dispels abnormal craving for food, and subtly elevates the mood. Reducing diets are accepted easily, without frustration.

'Methedrine' is safe, in recommended doses, for pregnant women.

'Methedrine' brand Methamphetamine Hydrochloride Tablet of 5 mg., scored.



BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

May, 1957

Page 43

*"But, Doctor, I must have olives . . . I'd starve without them!"*



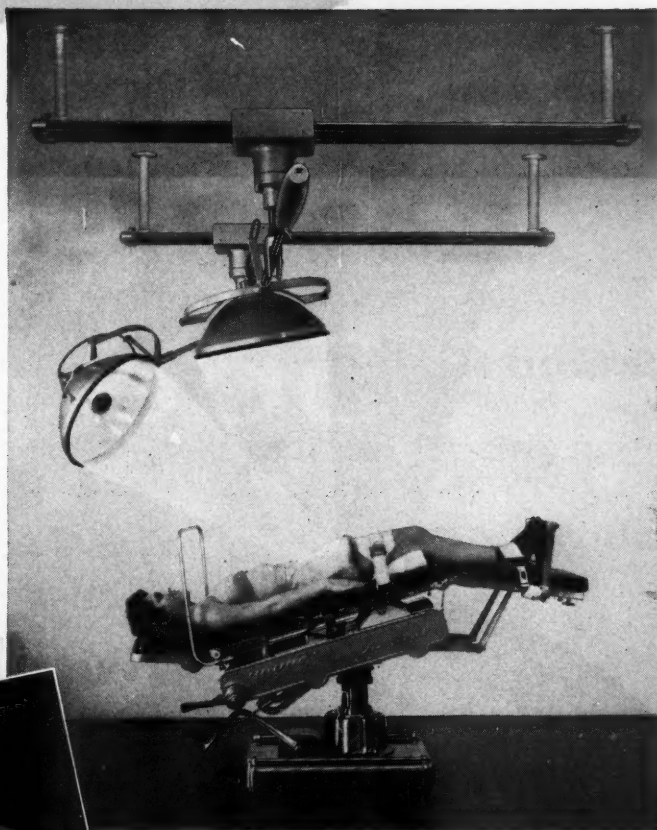
When a problem of weight control during pregnancy is complicated by bizarre eating habits, Dexamyl\* can often help your patient in two ways: (1) 'Dexamyl' controls appetite and (2) 'Dexamyl' "normalizes" eating habits by improving her mood and lessening her preoccupation with diet. 'Dexamyl'—a combination of Dexedrine\* (dextro-amphetamine sulfate, S.K.F.) and amobarbital—is available as tablets, elixir and Spansule\* sustained release capsules.

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\*T.M. Reg. U.S. Pat. Off.

**American** offers a **NEW**  
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The dual light sources are separately maneuverable through the full surgical range... with selective intensities of 1,000 to 12,000 foot candles and optional light patterns of 10", 6" or 4". Cool, glare-proof and color corrected, the DV-22 measurably raises the standards of illumination for general surgery and the specialties.



← Sterilizable handles... attachable at the center of each light beam... permit the surgeon to make fine directional adjustment, complementing remote control by the circulating nurse.

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MANUAL NUMBER C-161R

**AMERICAN  
STERILIZER**  
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Branches in 14 Principal Cities

**Iron Therapy--Well tolerated**

by

**555** out of

**563** patients

**ferronord<sup>®</sup>**

(brand of ferroglycine sulfate complex)



"555 (98½%) patients tolerated this ferrous sulfate-amino acid complex (FERRONORD) without complaint."<sup>1</sup>

"Extraordinarily well tolerated" in 120 obstetrical and gynecological patients.<sup>2</sup>

Well tolerated even in patients with peptic ulcer and gastritis.<sup>3</sup>

- serum response in 3 hours
- clinical response in days
- between-meal administration for better utilization

**FERRONORD Dosage:**

average adult dosage: Initially, 2 tablets twice a day; in severe cases, 2 tablets 3 times daily. Maintenance, 1 to 2 tablets daily.

children's dosage: In proportion.

**FERRONORD Supplied:**

Bottles of 100 tablets. Each tablet supplies 40 mg. of ferrous iron.

1. Frohman, I. P.; Pomeranze, J.; Rummel, W.; Kircher, R. F.; Clancy, J. B.; Dwyer, T. A.; Wagner, H.; O'Brien, T. E.; Curley, R. T.; Jörgensen, G.; Onorato, R. R.; Ira, F.; Lee, Jr., J. G.; Gorla, W. O.; White, R. N.; Gadek, R. J.; Remy, D.: Scientific Exhibit, 6th International Congress of Hematology, Boston, Mass., August, 1956.
2. Wagner, H.: *Landarzt* 31:496, 1955.
3. Jörgensen, G.: *Arztl. Wehnschr.* 10:82, 1955.

†α-aminoacetic-ferrous sulfate complex, exsiccated



**NORDMARK** PHARMACEUTICAL LABORATORIES, INC., IRVINGTON, N. J.

*Suppliers of fine chemicals to the pharmaceutical industry for more than a quarter of a century.*

# postpartum pain

effectively controlled  
for 10 to 12 hours  
on a single  
tablet



For the first time you can now prescribe extended action codeine. Donnagesic *Extentabs* offer the obstetrician the high level of codeine analgesia he needs<sup>1,2</sup> to help give a restful puerperium to the 75 per cent of multiparas who suffer after-pains.<sup>1</sup>

But more than extended codeine analgesia is provided by Donnagesic. Essential sedation<sup>1,3</sup> to reduce pain consciousness and anxiety is also provided, for Donnagesic contains the balanced ratio of natural belladonna alkaloids and phenobarbital of Donnatal®

Further, the phenobarbital augments the potent analgesia provided,<sup>4</sup> while the alkaloids minimize the possibility of codeine constipation, nausea and vomiting, which occasionally result from codeine administration.

1. DeLee, J. B., and Greenhill, J. P.: *Principles and Practice of Obstetrics*, Philadelphia, W. B. Saunders Company, 1948; p. 299.
2. Williams, W. J.: *Obstetrics*, Eastman, M. J. (ed.), New York, Appleton-Century-Crofts, Inc., 1950; p. 489.

DONNAGESIC	No. 1 (pink)	No. 2 (red)
CODEINE Phosphate ....	48.6 mg. (¾ gr.)	97.2 mg. (1½ gr.)
Hyoscyamine Sulfate ...	0.3111 mg.	0.3111 mg.
Atropine Sulfate .....	0.0532 mg.	0.0582 mg.
Hyoscyne Hydrobromide..	0.0195 mg.	0.0195 mg.
Phenobarbital .....	48.6 mg. (¾ gr.)	48.6 mg. (¾ gr.)

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**Extended Action:** The intensity of effect smoothly sustained ALL-DAY or ALL-NIGHT by each Donnagesic *Extentab* is equivalent to, or greater than, the maximum which would be provided by q.4h administration of one-third the ingredients stated in the formula.

3. Beck, A. C.: *Obstetrical Practice*, Baltimore, The Williams and Wilkins Company, 1947; p. 232.

4. Goodman, L. S., and Gilman, A.: *The Pharmacologic Basis of Therapeutics*, N. Y., The Macmillan Company, 1955; p. 187.

A. H. ROBINS CO., INC., Richmond 20, Virginia Ethical Pharmaceuticals of Merit Since 1878



# Donnagesic

*Extended action tablets of Codeine with Donnatal®*

# Extentabs

no call from  
pain tonight

Edwards, Iva (Mrs.)

Address  
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AB 4-4134

Occupation  
Laundry

Age  
43

JCM 484331

Ref. by Mrs. Wilson

2/4/57

Heavy set, works in hot environment, nylon bra. Eruption under breasts - folliculitis, 1 day - erythema, 3 days - eczematized eruption past week - pruritus, weeping, fissure. Has used several 'salves' and drying lotions, caused burning and spread.

FH-PH: No diabetes, systemic disease

Dx: Intertrigo, inframammary



Worth trying—

PRODUCT INFORMATION

TASHAN CREAM 'Roche'

SOOTHING, HEALING MULTIVITAMIN SKIN CREAM

DESCRIPTION: Tashan Cream provides four vitamins to help maintain skin health and promote healing.

Each gram (approx. 1/30 ounce) contains:

Vitamin A . . . . . 10,000 U.S.P. units  
Vitamin D<sub>2</sub> . . . . . 1,000 U.S.P. units  
d-Panthenol . . . . . 50 mg (5%)  
Vitamin E (d/-alpha-tocopheryl acetate) . . . 5 mg  
in a cosmetically pleasing, vanishing cream type base.

PROPERTIES: Vitamins A and D help maintain skin health; inhibit keratin formation; promote smoother, softer skin. Vitamin E is antipruritic; exerts a trophic effect through stimulation of skin metabolism. Panthenol is essential for integrity of tissue in general, promotes epithelization.

INDICATIONS: To relieve symptoms and promote healing in skin disorders characterized by itching, dryness, fissures, superficial ulceration, delayed cicatrization, etc., including:

Eczema	Nipple conditioning
Diaper rash	Minor burns
Prickly heat	Contact dermatitis
Intertrigo, chapping	Pruritus ani and vulvae
Sunburn, windburn	Diabetic skin disorders
Decubitus ulcers	Excoriation

DOSAGE: Apply a thin layer of Tashan Cream and rub in gently, three or more times daily.

PACKAGES: 1 ounce tubes.

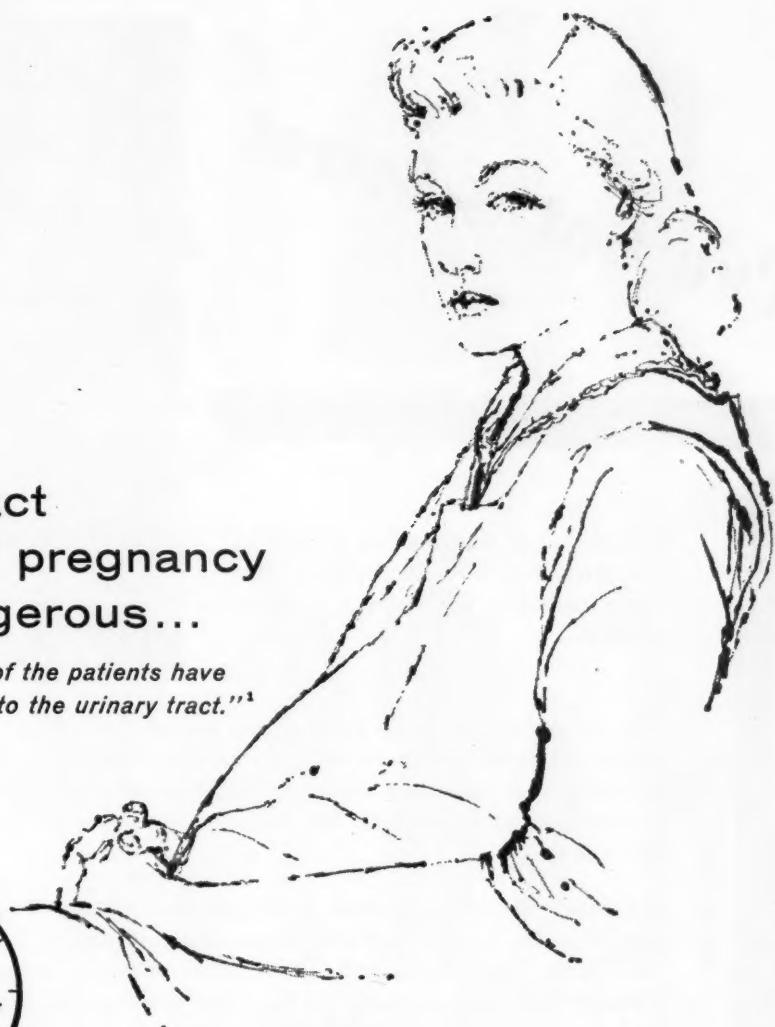
Tashan®

Hoffmann-La Roche Inc • Nutley • New Jersey



in urinary tract  
infections of pregnancy  
delay is dangerous...

*"Approximately one-half of the patients have  
some permanent damage to the urinary tract."<sup>1</sup>*



**FURADANTIN<sup>®</sup>**

BRAND OF NITROFURANTOIN

*first...*  
FOR RAPID ERADICATION OF INFECTION

Specific for genitourinary tract infections  
• rapid bactericidal action against a wide  
range of gram-positive and gram-nega-  
tive pathogens and organisms resistant to  
other agents • negligible development of  
bacterial resistance • excellent tolerance  
—nontoxic to kidneys, liver and blood-  
forming organs • safe for use in preg-  
nancy<sup>2,3</sup>

AVERAGE FURADANTIN DOSAGE: 100 mg.  
q.i.d. with food or milk. Continue treat-  
ment for 3 days after urine becomes sterile.

SUPPLIED: Tablets, 50 and 100 mg.  
Oral Suspension (25 mg. per 5 cc. tsp.).

REFERENCES: 1. Rives, H. F.: *Texas J. M.* 52:224, 1956.  
2. Diggs, E. S.; Prevost, E. C., and Valderas, J. G.: *Am.  
J. Obst.* 71:399, 1956. 3. MacLeod, P. F., et al.: *Inter-  
nat. Rec. Med.* 169:561, 1956.

**NITROFURANS**

a new class of antimicrobials—neither antibiotics nor sulfonamides

EATON LABORATORIES



NORWICH, NEW YORK

# I've Got a Secret

It's probably that he has a frog in his pocket... but his mother also has a secret... she's going to have a baby.



This intelligent modern mother has placed herself in the care of the physician in whom she has implicit faith. Now, the Doctor may, and probably does, prescribe a number of different prenatal supplements to his patients for various but valid reasons.

It is quite possible, indeed probable, that the physician may consider the use of a phosphorus-free, aluminum hydroxide containing product. Especially if it also provides organic iron, Vitamin B12 with intrinsic factor, plus the *important* vitamins in the *new* levels suggested for pregnant or lactating women. There are only a very *few* such quality formulas available for his choice.

One such formula with perhaps the easiest product name to remember on the national scene is Calcinatal<sup>®</sup> (*pronounced Calci' natal*) by Nion.

Patient acceptance of these easy-to-swallow tablets (not capsules) is quite understandable. Incidentally, one of your obstetrical problems, "control of Cramps" will be relegated to one of very minor incidence by use of the product. For more complete information, samples and brochure write to

**NION CORPORATION**  
LOS ANGELES 38, CALIFORNIA

**P.S.**

*We feel copy writers usually mention product names too often . . . we mention ours but only once. It is so easy to remember and hard to forget. Say it once - try to forget it.*



highly effective—clinically proved

# Sigmamycin\*

OLEANDOMYCIN TETRACYCLINE

provides added certainty in antibiotic therapy particularly for that 90% of the patient population treated in home or office...

Multi-spectrum synergistically strengthened SIGMAMYCIN provides the antimicrobial spectrum of tetracycline extended and potentiated with oleandomycin to include even those strains of staphylococci and certain other pathogens resistant to other antibiotics.

Supplied: SIGMAMYCIN CAPSULES — 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.), bottles of 16 and 100; 100 mg. (oleandomycin

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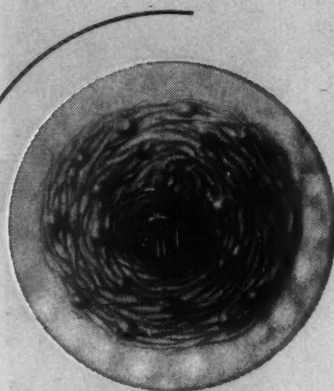
PFIZER LABORATORIES, Brooklyn 6, N. Y.  
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World leader in antibiotic development and production

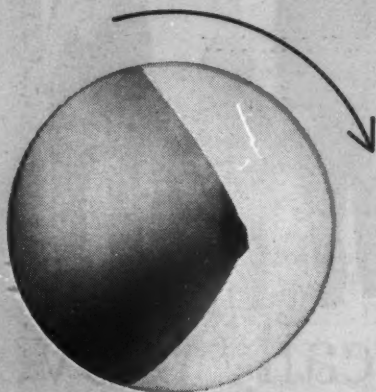


### FISSURED NIPPLE THERAPY

The use of White's Vitamin A & D Ointment soothes and softens the fissured nipple, promotes tissue regeneration.



## WHITE'S VITAMIN A & D OINTMENT

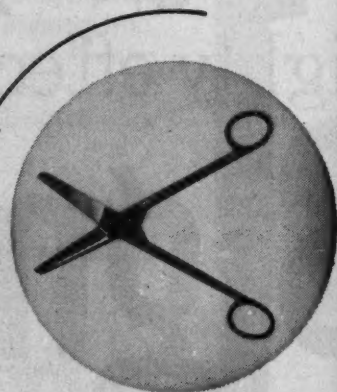


### NIPPLE ROUTINE

—a valuable and simple prophylactic measure against drying, fissuring and erosion.

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*for natural acceptance of your prescribed contraceptive regimen • fulfills your patient's natural wish that her possessions reflect her femininity. Each Lanteen Exquiset contains: 3 oz. tube of Lanteen spermicidal jelly, soothing, cleanly scented; easy-to-insert, molded, flat spring diaphragm; Easy-Clean applicator; universal inserter—all fitted into a stylish, soft plastic purse.*

Lanteen jelly contains ricinoleic acid 0.50%, hexylresorcinol 0.10%, chlorothymol 0.0077%, sodium benzoate and glycerin in a tragacanth base. Lanteen jelly and flat-spring diaphragm sets are distributed by George A. Breon & Company, 1450 Broadway, New York 18, N.Y. (In Canada: E. & A. Martin Research Ltd., 20 Ripley Ave., Toronto, Canada.) Manufactured by Esta Medical Laboratories, Inc., Chicago 38, Ill.

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Each contains 100 mg. Colace  
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Dosage: 1 or 2 capsules at bedtime  
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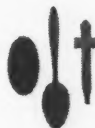
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1. Dieckmann, W. J., and Priddle, H. D.: Anemia of Pregnancy Treated with Molybdenum-Iron Complex, *Am. J. Obst. & Gynec.* 57:541, (March) 1949.
2. Neary, E. R.: *Am. J. Med. Sci.* 212:76 (July) 1946.
3. Kelly, H. T.: *Pennsylvania M. J.* 51:999 (June) 1948.

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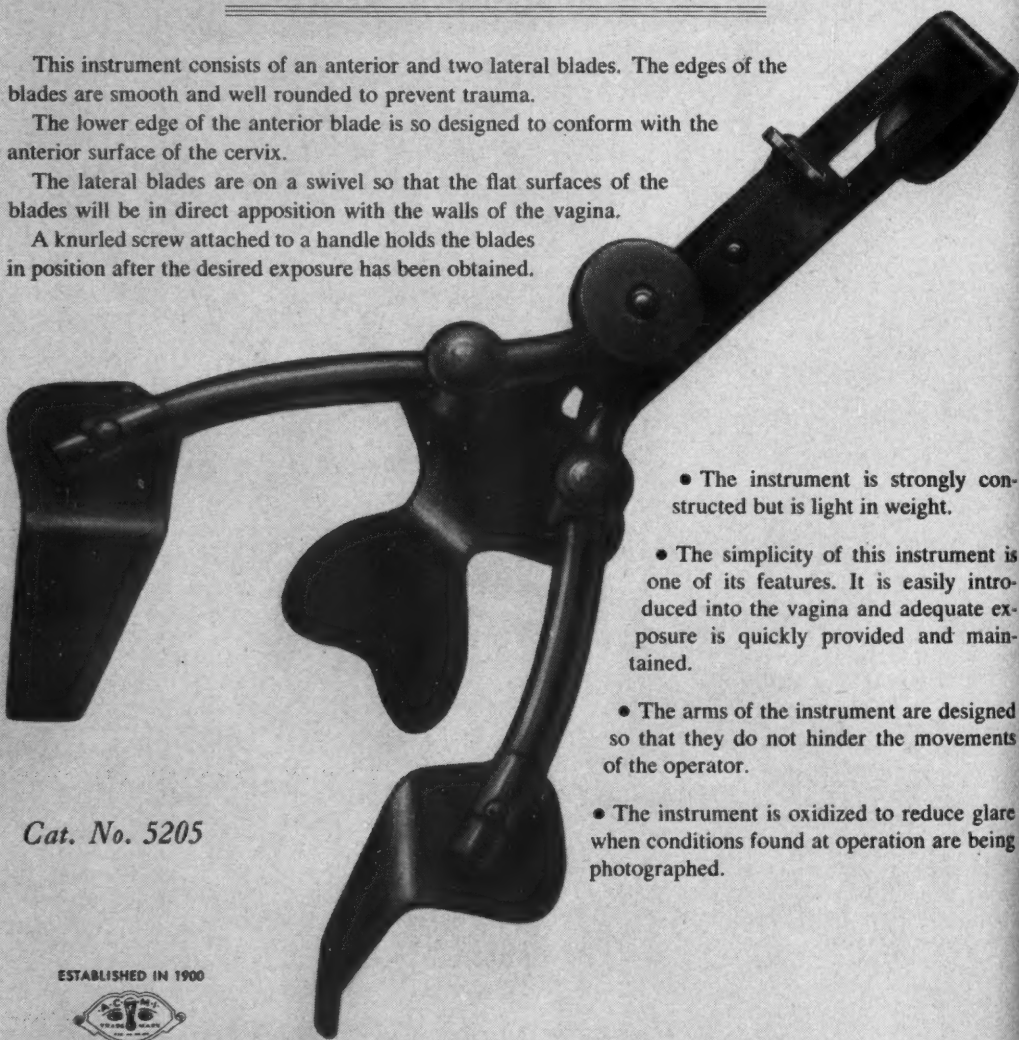
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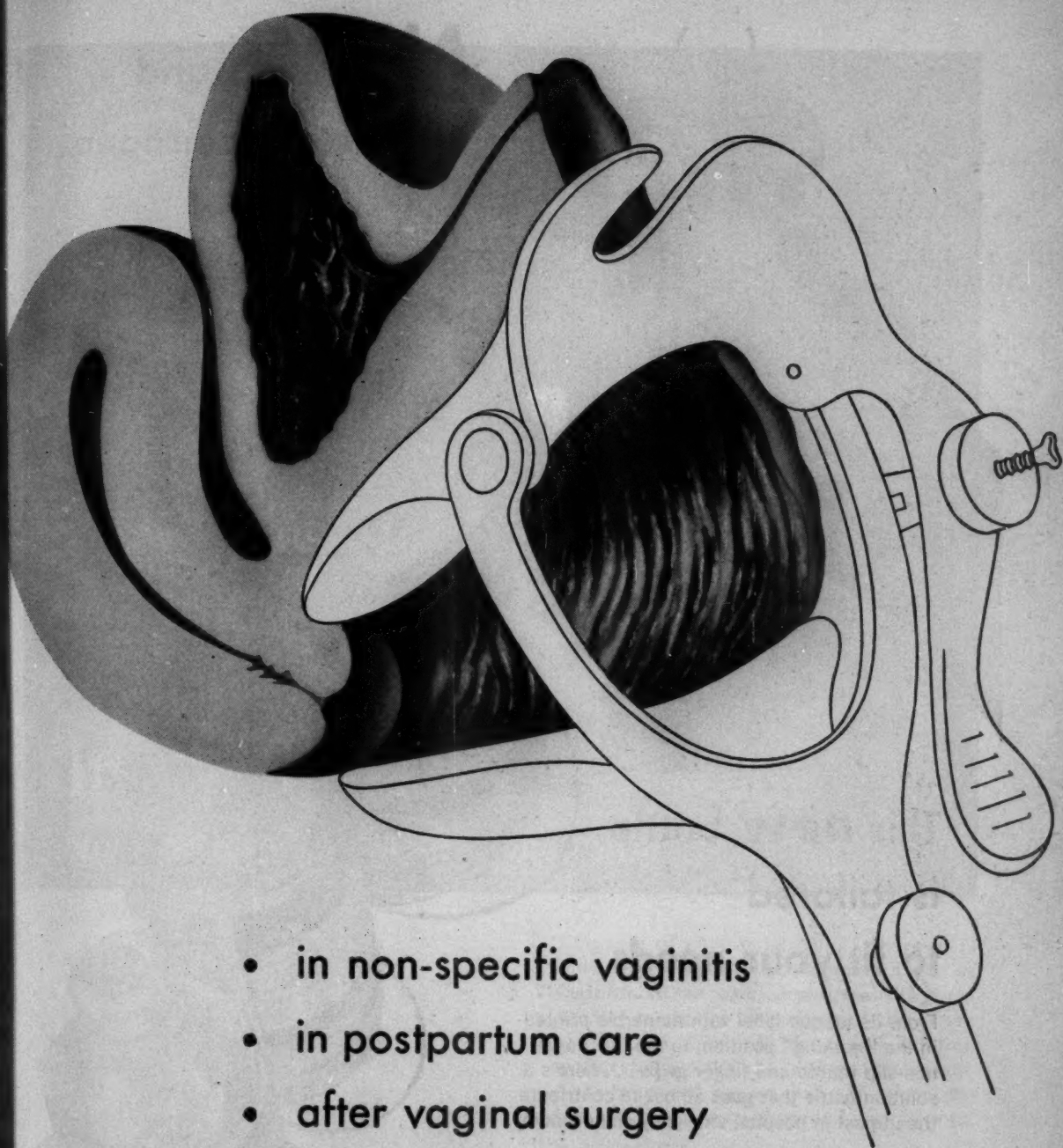
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- in non-specific vaginitis
- in postpartum care
- after vaginal surgery

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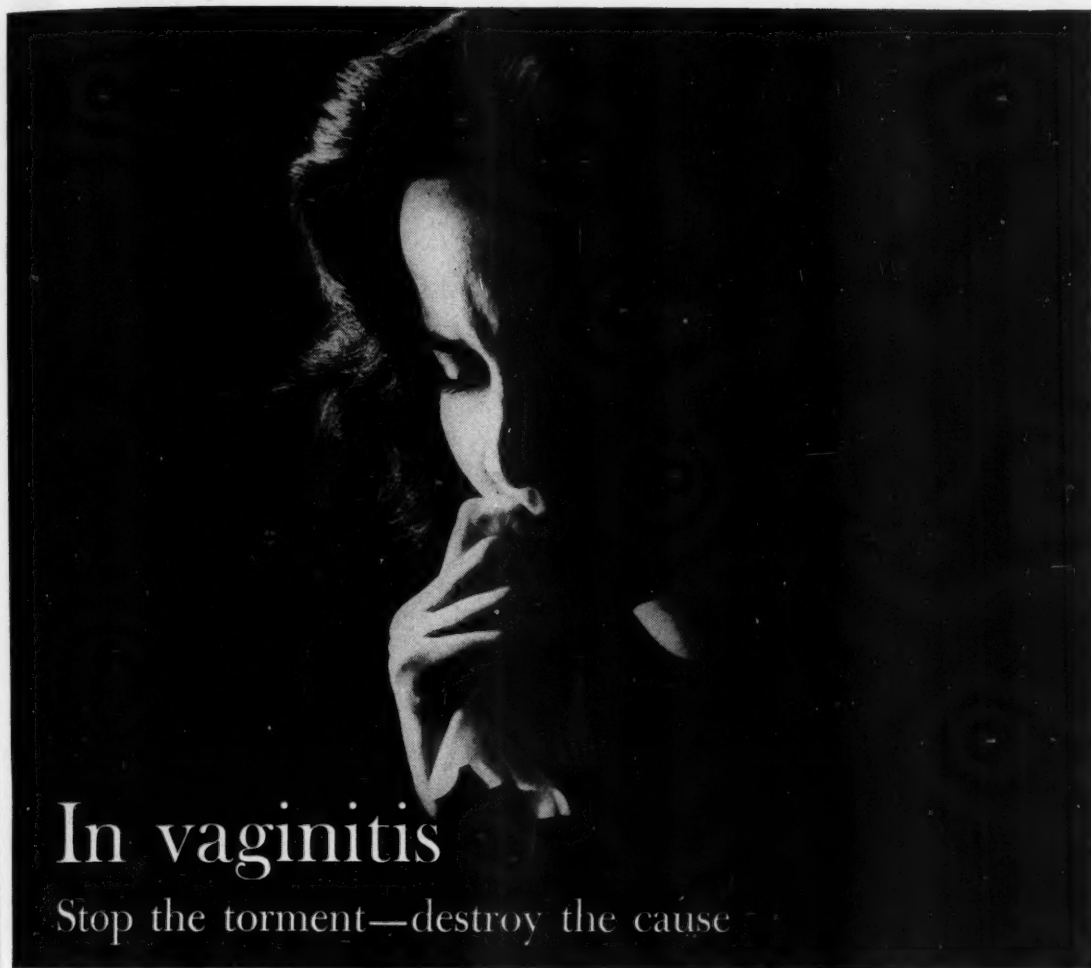
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*Improved*



**in trichomonal vaginitis —**  
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(1) Cortese, J. T.: Clin. Med. 2:45, 1955. (2) Hensel, H. A.: Postgrad. Med. 8:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

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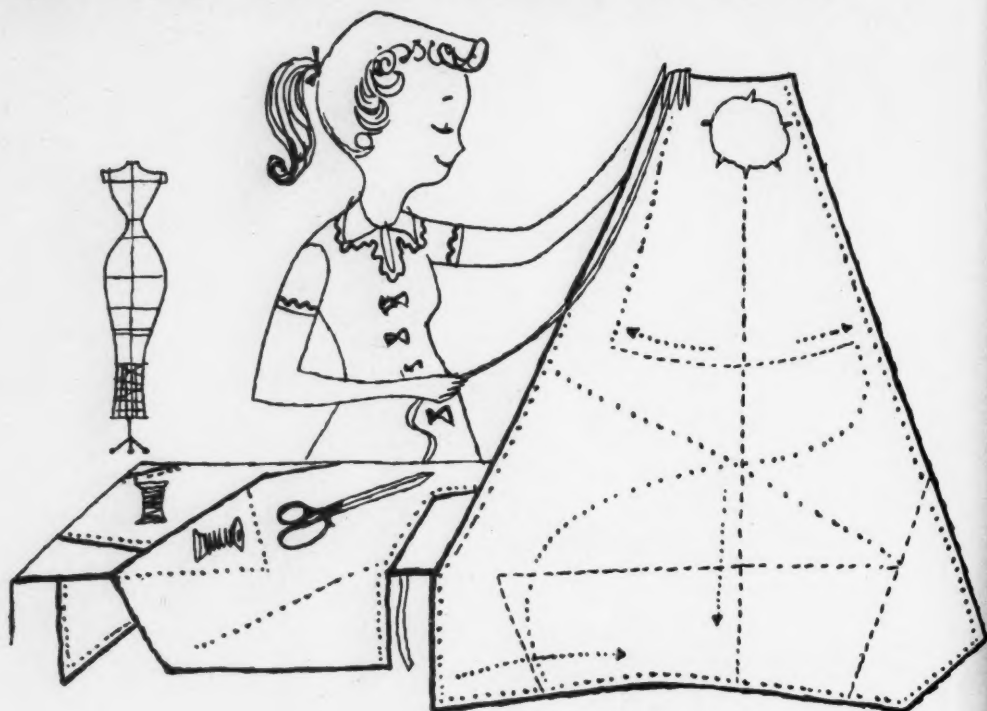
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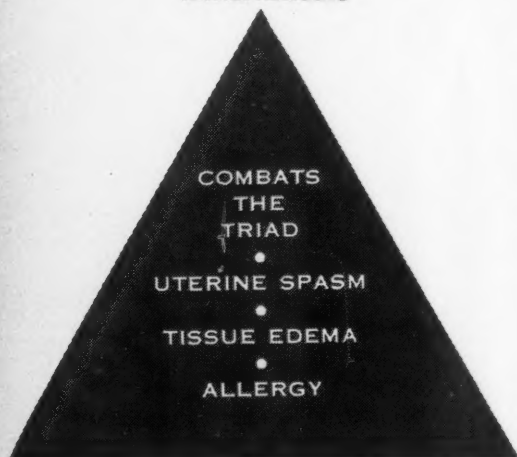
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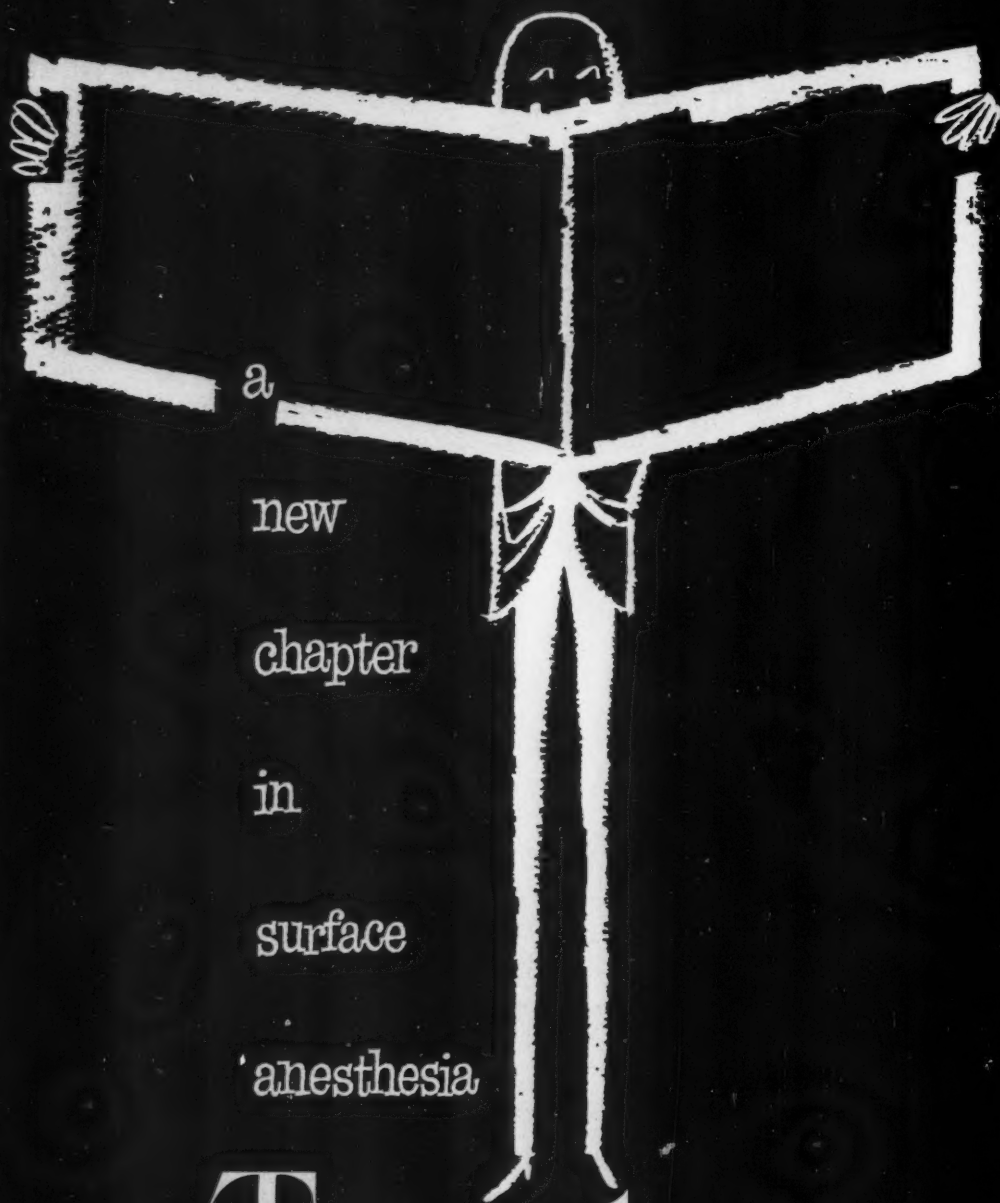
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*intravenous anesthetic*

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(1) Boone, J.D.; Munoz, R., and Dillon, J.B.: *Anesthesiology* 17:284, 1956. (2) Zima, O.; von Werder, F., and Hotovy, R.: *Anaesthesist* 3:244, 1954. (3) Fitzpatrick, L.J.; Clarie, D'A.C., and Mersch, M.A.: *Anesthesiology* 17:684, 1956. (4) Blake, M.W., and Perlman, P.L.: *J. Pharmacol. & Exper. Therap.* 117:287, 1956. (5) Ayd, F.J., Jr.: *Neraval: A new anesthetic for electroconvulsive therapy*, Paper presented at annual meeting, Electroshock Research Association, Chicago, Illinois, April 29th, 1956. (6) Irwin, S.; Stagg, R.D.; Dunbar, E., and Govier, W.M.: *J. Pharmacol. & Exper. Therap.* 116:317, 1956. (7) Reifferscheid, M., and Dietmann, K.: *Deutsche med. Wchnschr.* 79:638, 1954. (8) Dietmann, K.: *Deutsche med. Wchnschr.* 79:1748, 1954.

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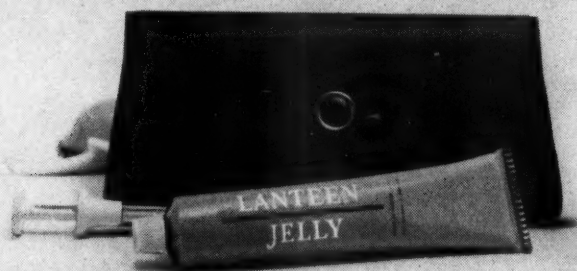
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May, 1957

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*Surgery That the Gynecologist Should Master!*

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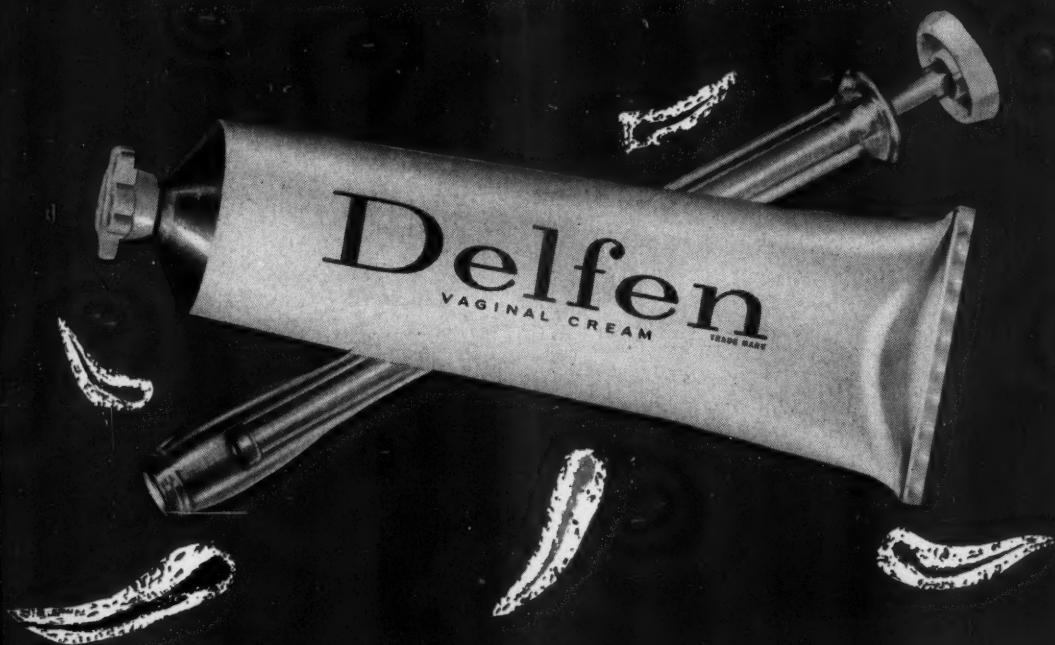
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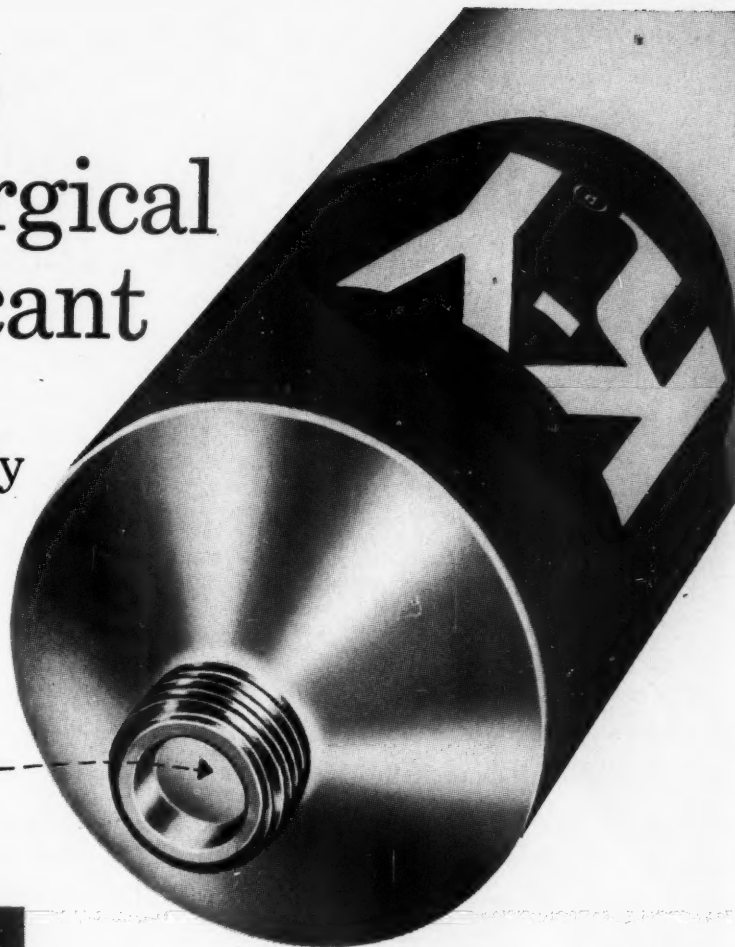
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**Guest Editor, Joseph J. Bunim, M.D.**

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							1	2
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11:52		OUT						
12:37		IN						
5:12		OUT						
		IN						
		OUT						
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8:59		IN						

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*Transactions of the Central Association  
of Obstetricians and Gynecologists, Twenty-fourth Annual Meeting  
New Orleans, La., October 4, 5, and 6, 1956*

## THE PLACENTA IS ONLY OUT OF SIGHT\*

CLYDE L. RANDALL, M.D., BUFFALO, N. Y.

OUT of sight" might imply that we cannot see, a handicap few could face without a feeling of helplessness. In the optician's window, a sign often reads, "Your eyes are your most precious possession—take care of them."

Thinking of what life would be if we could not see, we *are* likely to feel that our eyes are indeed life's most precious possession. Yet it is not man's eyes that have made him master of the planet we share with so many forms of life. Some birds and some animals have better vision. Because many of us see poorly, we may even wear glasses—and become amusingly dependent upon them. To the satisfaction of the optician, I am sure, we are not likely to forget how important it is that we be able to see. But let us not forget that to see, while important, is not quite our most precious possession.

Webster<sup>28</sup> defines man as "An individual of the genus *Homo* . . . the highest type of animal existing or known to have existed . . . differs from other animals more in his extraordinary mental development than in anatomical structure. . . . Man alone has . . . the capacity of abstract reasoning."

If we are to satisfy Webster's definition, obviously we must do more than use our eyes, though observation of all that we can see is an important first step. Eventually, remembering what we have seen, and with the gift of more than eyes to work with, we may comprehend an answer though the problem be out of sight where, literally, we cannot see.

Time does not permit tribute to the investigators among us, and before our time, whose ability to see clearly provides us with the knowledge by which

\*Presented at the Twenty-fourth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 4, 5, and 6, 1956.



we teach and practice obstetrics and gynecology today. The scientific mind, by objective study and accurate observation, might well be regarded as our very eye and, as such, perhaps our most valued possession. The years have convinced us that well-documented studies rarely lead us to steps that must later be retracted. It is still a temptation merely to try to dream up the answer, however, and today I would like to tempt you to run ahead of convincing studies for at least a time, even though we may not be able to see at all clearly as we go.

It seems timely to attempt a more all-inclusive concept of the risks inherent in placental deficiency than is evident in the dangers attributed merely to the prolongation of gestation.

In New York City, Gold<sup>14</sup> has recently reported that neonatal deaths (under 1 week of age) now average 16.2 per 1,000 births; of these, prematurity accounts for 51 per cent and malformations 15 per cent. Trauma related to birth accounts for 1.7 deaths per 1,000 births (10.5 per cent of the neonatal mortality), whereas erythroblastosis and anoxia together account for another 11 per cent. Antepartum and intrapartum deaths total 13.9 per 1,000 births, of which maternal disease and the complications of labor were considered responsible for only 20.4 per cent. Pathology of the fetus, placenta, or cord accounted for 25.8 per cent of such fetal deaths. Of chief interest, however, was the fact that 41.6 per cent of the total number of stillbirths studied by Gold were considered due to "ill-defined or unknown causes."

For years we have recognized that what is now termed perinatal mortality has included fetal losses due to a variety of difficulties. We have been occupied with the care of premature infants and with a considerable effort to reduce *neonatal* deaths. Stillbirths of macerated infants are often considered "correctable" in reports of fetal mortality, and intrapartum as well as antepartum deaths have received relatively little attention. With wider recognition of the fact that fetal deaths due to anoxia now account for 20 to 35 per cent of present-day perinatal loss, greater interest is now being evidenced in the possibly preventable causes of stillbirth.

It is generally recognized that such well-established examples of acute placental deficiency as placenta previa and premature separation may deprive the fetus of oxygen with overwhelming, fatal abruptness.

The low-lying, posteriorly implanted placenta described by Stallworthy<sup>26</sup> as "the dangerous placenta" is generally recognized as a potential source of maternal hemorrhage. It also threatens as a potential source of fetal asphyxia. Even though a significant area of placenta does not separate prematurely, the cord or its site of attachment may be compressed between the sacral promontory and the advancing fetus.

A less frequently recognized source of placental dysfunction which may contribute to an occasional fetal death has been emphasized by Browne<sup>4</sup> who believes, when the membranes rupture early and a considerable quantity of the fluid escapes from the uterus, that some retraction of the uterus may result. The area of the placental site and the volume of maternal blood circulating through it are thus diminished, a possibility he regards as one of the real dangers of "long first stage."

Several clinical entities have long been recognized as apparently predisposing to death of the fetus near term or during labor. The risks of being prematurely born are generally recognized. Anderson and Nesbitt's<sup>1</sup> recent report from the Hopkins Hospital indicates that, during the period Jan. 1, 1937, to Dec. 31, 1949, premature infants comprised 11.2 per cent of the total



(26,776) births but accounted for 54 per cent of the total perinatal mortality. During the same 13 year period there were 83 deliveries in the 400-999 gram "immature" group, of which number 76, or 91.6 per cent, failed to survive.

Certain dangers have also been described when pregnancy is prolonged beyond the usual period of gestation, but such an entity as postmaturity has long been a source of dispute. Ballantyne<sup>2</sup> was perhaps the first to note "that premature babies can with difficulty be kept alive after birth, whereas the postmature child can with difficulty be born alive." He also suggested that in the management of labor, in both instances, we should consider that "hurry is bad, but delay is very bad—let us have deliberateness but not procrastination." He found it difficult, of course, to fix the date of maturity. "It is impossible," he wrote, "to fix exactly the date of pregnancy when an infant begins to be postmature, and impossible to state the time beyond which an infant can no longer be retained alive in the uterus." He concluded, however, that: "(1) A prolonged pregnancy need not necessarily result in the birth of a postmature infant. (2) Neither the dimensions of the fetus, nor the degree of development of his tissues and organs, nor the history of the pregnancy can be regarded as certain proof of postmaturity. (3) There is an unusual incidence of anencephalic monsters; absence of the lanugo and of the vernix; the nails project well beyond the tips of the digits; ossification is far advanced. (4) The amniotic liquor is small in amount, in some cases nearly absent, and the placenta does not keep up with the increasing weight of the baby during its added time in the uterus." In discussing the management of postmaturity, Ballantyne suggested, "as with the premature, so with the postmature . . . the ideal plan of procedure is *prevention*."

Many of the same convictions are being emphasized today, yet Ballantyne's description of postmaturity was published in 1902! Considering the toll that dysfunctions of the placenta must have caused during 54 intervening years, it is evident that, if we are now wiser, such realization has come late. Too many of us have for too long willingly assigned too many antepartum and intrapartum deaths to the category of "ill-defined or unknown causes." Too long we have spoken of fetal injury in terms of trauma and cerebral hemorrhage. This concept has no doubt been largely responsible for the obstetrician's failure to appreciate some of the real hazards of childbirth. So long as we could think in terms of trauma, so long could we smugly feel confident that in competent hands fetal injury would not occur.

Nesbitt,<sup>1</sup> reviewing the term deliveries at Johns Hopkins Hospital during the four years 1950-1954, in a total of 7,415 supposedly term births, considered 812 as prolonged pregnancies, indicating an 11 per cent incidence of so-called "postmaturity." Perinatal mortality in this postmature group was three times what it was among the infants born at term. Although this increased death rate was due to deaths occurring before the onset of labor, during labor, and during the neonatal period, a significantly increased proportion of fetal deaths occurred during labor. Considering the intrapartum deaths, Nesbitt noted a six times greater incidence of intrapartum deaths when pregnancy had been prolonged. Ballantyne and Browne had both expressed belief that postmaturity carries an increased risk chiefly because of relative disproportion due to the excessive size of the postmature baby, for which reason they had advocated induction of labor at term to avoid the dangers of such disproportion. Calkins<sup>5</sup> in 1948 and Mills<sup>22</sup> in 1955, on the other hand, had concluded that fetal growth usually does not continue after the fetus reaches term, and expressed belief that as the placenta ages its efficiency decreases, to a point where the baby may actually begin to lose weight.

Calkins has reported that placental weight and baby weight increase rapidly up to about day 260. Growth is less rapid from the two hundred sixtieth to the two hundred eightieth day, and any increase after full term is very small. He has long believed that the size of the placenta is more likely to determine the size of the baby than is postmaturity per se. He has also expressed belief that an oversized infant will have acquired most of its excessive size by about the two hundred sixtieth day of gestation, so that by full term any further increment in its size will be so slight as to make no real difference in the conduct of the subsequent labor. He emphasized that the disadvantages of induction of labor in the presence of an unprepared cervix cannot possibly be justified on the basis that the child would be getting larger if it continued to grow into "postmaturity." In 1948, Calkins concluded that it was still advisable to agree with Rudolph Holmes<sup>15</sup> that "there is no postmaturity problem." Kamperman,<sup>17</sup> agreeing with Calkins, expressed the belief that statistics could be shown to indicate that, if pregnancy is prolonged beyond the twentieth day (i.e., 280 plus 20 days) the baby begins to lose weight and that, at least statistically, the longer postmaturity continues after the twentieth day, the smaller will be the baby!

It seems impossible that we have been so slow to emphasize the importance of maintaining oxygenation of the fetus during the pressures and difficulties of labor. Eastman<sup>9</sup> has likened the fetus to the climber scaling Mount Everest. In an atmosphere of oxygen want, the fetus, like the high climber, is obviously dependent upon a lifeline of oxygen; when interruption occurs, or the supply is exhausted, permanent damage or death occurs. All agree that the fetus depends for its growth and development upon an adequate supply of nutrients received by way of the placenta, but Walker<sup>27</sup> reminded us that oxygen is unique among such nutrients, in that it cannot be stored and must be continually supplied. Walker has also emphasized the probability that decrease in the oxygen supply, due to changes in the placenta as pregnancy becomes prolonged, is the causal factor in the deaths of many so-called "postmature" fetuses, and concludes that quantitative estimations of fetal oxygen lend definite support to those who, on purely clinical grounds, have continued to believe that postmaturity may be dangerous.

Gibson<sup>13</sup> had also concluded that trauma is not a significant factor in the death of postmature babies. Since many such fetal deaths occurred without evident cause, they were generally regarded as a somewhat mysterious, ill-defined group. He admitted, moreover, that Gibberd<sup>12</sup> and Clayton<sup>7</sup> were probably right in assuming that such strange, ill-defined deaths as are often seen in postmaturity may well be due to anoxia, particularly since Walker in 1954 had produced experimental evidence to support the growing belief that the risk of postmaturity is essentially but the risk of intrauterine hypoxia.

Gibson's<sup>13</sup> total incidence of pregnancies prolonged for more than 14 days beyond the estimated date of confinement was 7.4 per cent. Believing that the induction of labor is risky when postmaturity is suspected, he advised "masterly inactivity" until labor starts, after which the strictest watch for fetal distress is indicated, with resort to cesarean section at once in cases in which fetal distress becomes evident. He emphasized that fetal mortality, while minimal during the forty-first and forty-second weeks, doubled during the forty-third week, and tripled thereafter. On this basis he concluded that prolonged pregnancy is pathological and significant. He could not, however, find evidence to support Malpas<sup>21</sup> belief that a number of deaths of postmature infants were in reality due to fetal abnormalities.

More recently, Calkins<sup>5</sup> concluded that the dangers of postmaturity should be considered when the baby (and therefore most certainly the placenta) appears to be surprisingly small and seemed impressed by the fact that he had noted no deaths from placental causes when the baby was large.

Clifford<sup>8</sup> has repeatedly described the baby born some weeks after the expected date of confinement, who appears to be of less than average weight at term but is occasionally more than 21 inches (53 cm.) long; who has a loose skin suggestive of dehydration and possibly of weight actually consumed in utero, and skin, cord, and amniotic fluid usually stained yellow to brown. This is now a widely recognized entity. Such a child is often born dead or, if born alive, seems predisposed to respiratory distress. Smith<sup>24</sup> believed that many, if not all of the unusual features of the infants Clifford described could result from inadequate placental function, and might well be anticipated when pregnancy is prolonged, since Flexner and Hellman<sup>11</sup> have shown that the human placenta becomes less permeable after its peak of function at 36 weeks. Clifford reported that in their experience prematurity, with an incidence of 9 per cent, accounts for 36 per cent of perinatal deaths, whereas postmaturity, with an incidence of 6 per cent, accounts for 30 per cent of their perinatal deaths. He emphasized that postmaturity is a particular hazard to the primigravida, for he found that when a first pregnancy is prolonged beyond the three hundredth day of gestation, one in every 10 of the infants dies. He also noted that, in their study, 73 per cent of the primigravid patients whose period of gestation lasted 300 days or longer did not again become pregnant during a 10 year period of follow-up.

If we are to broaden our concept to include other causes of ill-defined fetal deaths, we might well begin by a brief consideration of what has been referred to as the "habitual death of the fetus." Occasionally, with no evidence of disproportion and an apparently normal baby at term, heart sounds would disappear during the latter part of the first stage or during the second stage of labor, followed by the delivery of a perfectly normal but stillborn fetus. Older clinicians were particularly impressed by the possibility that such an unexplained intrapartum fetal death might recur in the same individual in subsequent pregnancies.

In an example of the situation classically regarded as due to an "inadequate placenta," pregnancy would again seem to be progressing normally. Late in the eighth or early in the ninth month of gestation, though her last prenatal appearance had suggested that the baby was still small, the patient would report the rather abrupt onset of frequent pains. On admission to the hospital, the heart sounds could not be heard. Rapid progress was apparent and as the membranes ruptured only a small amount of highly stained amniotic fluid was noted. At delivery, the stillborn fetus appeared surprisingly small, with a noticeably small, atrophic-looking placenta. In connection with such a case, with no signs of renal disease or of syphilis, Foster Kellogg<sup>18</sup> talked of "premature aging of the placenta," typified by a rapid labor, highly colored fluid, a stillborn baby obviously small, with an avascular looking placenta only one eighth or one tenth of the weight of the small fetus.

Did this entity represent premature aging of a formerly normal and adequate placenta, or was the placenta always smaller than the usual ratio? The possibility of inadequacy from the earliest stages of placental development became evident by 1950 in the work of Smith and Smith.<sup>25</sup> Hughes<sup>16</sup> emphasized that endometrial deficiencies may account for inadequate nutrition in the very earliest critical stage of implantation, with resulting abnormalities of development of both decidua and embryo. In cases of habitual abortion, he has always favored treatment before conception, whereas the



Smiths have emphasized the postconceptional addition of increasing amounts of stilbestrol, both attempting to assure adequacy of the placenta. In recent years, it has seemed reasonable to believe that even a normal placenta might become inadequate, particularly if pregnancy is prolonged and the placenta and fetus become postmature. This concept has been strengthened by the many current studies of anoxia during labor, particularly by the data indicating the danger of fetal anoxia if pregnancy is prolonged or uterine contractions seem unusually frequent and severe.

There is reason to be apprehensive for the patient who experiences difficulty becoming pregnant and then seems to be "behind schedule" in the last trimester. A smaller than expected baby as term approaches may certainly indicate inadequacy of the placenta, and a situation in which a poorly nourished child will be deprived of oxygen to a dangerous degree as soon as uterine contractions become established. There is no situation in obstetrics where alert attendants and a good obstetrician are more essential. We all recognize the possible consequences of induction of labor when the cervix is not ripe, or of cesarean section *when the child is really normal but immature*. So also must we recognize the consequences of permitting a poorly nourished, poorly oxygenated, smaller-than-expected baby to survive the hypoxia of the labor that can be anticipated when the placenta is inadequate or postmature.

A present tendency is to consider the anoxia which causes intrapartum fetal deaths and that which causes central nervous system injuries among infants who survive birth as one and the same thing, differing only in the degree of damage sustained by the fetus. Regarding the advisability of continued efforts at resuscitation of the severely asphyxiated baby, the *British Medical Journal*<sup>3</sup> has recently admitted that, as the minutes go by, the damage which the child's nervous system may have sustained should indeed cause concern, but agreed that so long as the fetal heart continues beating the child is entitled to the possible benefit of our continued effort. The *Journal* emphasized, moreover, that it is well to assume in resuscitating a newborn infant that one is fighting not only for the child's life, but for its very wits, and concludes that no technique of resuscitation at birth can promise as much as the prevention of the need for it in the first place.

It is now evident that short, precipitous delivery means long periods of uterine contraction, materially reducing blood flow across the placenta. Such relative apnea may be extremely dangerous for the fetus, particularly if labor begins when the child is premature or when a fully mature baby is depending upon a poorly functioning, postmature placenta for oxygen.

Since we now recognize that fetal death is more likely to be caused by asphyxia than by trauma, no phase of the management of labor is more important than early recognition of fetal distress. As a rule, we must depend upon changes in the fetal heart sounds to indicate impending or established fetal distress.

In spite of the observations of Lund<sup>20</sup> and Cannon,<sup>6</sup> Fitzgerald and McFarlane<sup>10</sup> have accepted the criteria set by Von Winckel: "(1) that fetal heart rates above 150 are significant, (2) that variations in the fetal heart rate during and following uterine contractions constitute a valuable and early sign of fetal distress, and (3) that all cases with meconium in the amniotic fluid in cephalic presentation, even if staining only is present, should be reported promptly to the staff, and that thereafter (4) the fetal heart rate should be charted in graphic fashion."

The same observers noted no significant difference in the incidence of fetal distress among mothers over 30 as compared with those under 30 years of age. They did find, however, that the incidence of fetal distress was 8.9 per cent in



primigravidas, whereas the incidence of a similar degree of distress was only 4.6 per cent in multigravidas. When antepartum bleeding had been recorded in the patient's history and the child was alive at the onset of labor, Fitzgerald and MacFarlane<sup>10</sup> thought that some degree of placental inadequacy might be anticipated, for they noted in cases where bleeding before the onset of labor had been recorded that fetal distress was evident in 13.1 per cent of cases, as compared with 6.1 per cent when there had been no such bleeding.

In a careful survey of 100 cases of fetal distress, representing 6.6 per cent of all the deliveries reviewed, Whitehouse<sup>29</sup> concluded that quickening of the fetal heart sounds followed by marked slowing of the rate was of the greatest significance, and indicated a gravely asphyxiated fetus. He suggested that recording of the fetal heart rate every 20 minutes during the first stage and every 10 minutes during the second stage should be routine in all labors. Although Whitehouse believed that intrauterine death during labor may occasionally occur without warning, he felt that such cases are rare, that fetal sounds will usually give ample warning when danger threatens. Malpas,<sup>21</sup> however, emphasized that there may be no warning of impending intrauterine death, and concluded that fetal distress is better anticipated than diagnosed.

### Management of the Patient

Management of the patient is a subject quite beyond the limits of this discussion, but a few comments seem timely. Walker<sup>27</sup> suggested that we should induce labor before the fortieth week in cases of pre-eclampsia or in those in whom bleeding has occurred in the early months of pregnancy (when inadequacy of the placenta should first be suspected). He allowed primigravidas under 25 years of age, with otherwise normal pregnancies, to go into labor spontaneously, but believed that induction should be considered if, after the expected date of confinement, the mother's weight decreases, the amniotic fluid appears to be lessening, or signs of pre-eclampsia develop. He believed that labor should be induced in primigravidas over 25 years of age at the end of the forty-first week of pregnancy, and if, when the membranes rupture, the fluid is stained with meconium, that elective section should be promptly performed; that slowing of the fetal heart as a sign of fetal distress may not occur at all, or may be too late to provide reliable evidence of impending anoxia. For multigravidas, Walker believed that cesarean section is rarely indicated, but that induction at the end of the forty-first week should be considered, except when there is a history of a previous stillbirth, when labor might better be induced before term.

One word of caution! It seems evident from the standpoint of the child that induction may not be safe simply because labor can be easily induced. Labor may be more difficult to induce in the patient whose placental function is not impaired, but she is less likely to go into the precipitous type of labor that can be so damaging to her child. It is ironic, but it must be true, that the patient whose uterus is found to be most responsive to Pitocin might well be the one whose poorly functioning placenta will not provide sufficient oxygen to the baby once adequate uterine contractions are established.

Perhaps the patients in whom labor is most easily induced should have cesarean sections, and the ones who evidence resistance to Pitocin should be recognized as safer for induction! A trial of dilute Pitocin has been recommended as such a therapeutic test and may prove to be an invaluable aid, if the fetal heart sounds are carefully evaluated during and following contractions of the uterus as the Pitocin-induced pains begin.

Editorially, the *British Medical Journal* recently concluded that analgesic drugs commonly given to the mother during labor seldom cause fetal asphyxia,

though they do commonly depress respiratory activity after birth, whereas drugs which may have been used to expedite labor may readily provoke signs of fetal distress.

As soon as fetal distress appears, the *Journal* recommended that the mother be given pure oxygen, but emphasized that the employment of oxygen is only a temporary aid. Walker<sup>27</sup> admitted that the oxygen supply to the fetus could not be measured as a practical guide to the management of individual cases, and he also recommended that treatment be based on careful clinical assessment.

Nesbitt<sup>1</sup> has recently concluded that the difficulties encountered in establishing the diagnosis of postmaturity make any routine management a hazardous undertaking. He believed that emphasis should be placed on intelligent management as labor begins in cases of apparently prolonged pregnancy, rather than upon the routine induction of labor at some arbitrarily chosen week of gestation.

It is evident that similarly good judgment is necessary in the management of any pregnancy in which an inadequate placenta might be suspected, and it appears that we might well suspect inadequacy of the placenta whenever:

1. There is a history of infertility, of previous abortion, premature labor, abruptio placentae, toxemia, or an unexplained stillbirth.

2. Abortion threatens in the first trimester, or bleeding occurs in later pregnancy.

3. Toxemia develops.

4. Fetal growth does not seem "up to schedule" in the last trimester of pregnancy and the possibility of an error in estimating the probable date of confinement is considered. Then must we decide whether "we are a month off" in our calculation—or whether the fetus *has* stopped growing.

5. Labor fails to begin and pregnancy seems prolonged more than two weeks beyond what appears to be a correctly estimate date of confinement. The probability of placental inadequacy is increased if the size of the uterus seems to be diminishing and fetal parts become more easily palpable.

6. Rupture of the membranes in early labor shows discoloration or a decreased amount of amniotic fluid, and particularly whenever fetal heart sounds are found to vary noticeably with uterine contractions. There are differences of opinion regarding the significance of a fetal heart rate above 160 per minute, but considerable agreement that danger is evident when the fetal heart rate drops below 100 per minute during uterine contractions, particularly if it fails to resume a faster rate rapidly as each contraction diminishes.

Kramer<sup>19</sup> has recently mentioned five additional factors which he believes predispose to the development of fetal distress, namely, hypertension, cardiac disease, pulmonary disease, prolonged labor, incoordinate uterine action, and pyrexia during labor. He believes that all such patients should be put on prophylactic oxygen early in labor, and finds in his own practice that this results in the administration of oxygen during labor to approximately 15 per cent of the patients.

#### Comment

So long a list of the indications of placental deficiency seems impractical. We might well ask whether it is necessary to consider the possibility of placental deficiency all of the time, in all of its possible manifestations, if we are to recognize the first signs, anticipate the dangers, and avoid the consequences

of an inadequate placenta. Is there reason to feel that such vigilance is our obligation? Does human reproduction require such careful observation, so alert and so intelligent an obstetrician?

In the light of this evidence that many babies die at the onset of labor or during labor, because an inadequate placenta, or because a hypertonic uterus deprives the fetus of oxygen, Walker concluded that confidence in the probability of an ideally normal and easy "natural childbirth" is not justified. He advocated close supervision of pregnancy and labor, because he believed that in modern society there is no longer a natural selection, or the perpetuation only of women best suited to reproduction. It is ironic but true that the better the obstetrics practiced in a given area, the less the chances that natural selection will assure predominance of those women most physiologically suited to childbearing in each succeeding generation; as a result of better obstetrics, in all probability, each generation of obstetricians will care for a greater number of women who, for one reason or another, are not well suited to reproduction.

Today we see many women with a history of infertility or repeated abortion, and others who have lost a child nearly at term, or at term, or in the first few days of life. If we are going to assure them that they should try again, and that with our help they will this time succeed, then we will have to accept the burden of watching them so closely as to recognize signs of placental inadequacy, at whatever stage of pregnancy it threatens.

We are trying to make certain that among each 100 women admitted for delivery, not two, but only one, will go home without a normal child. We *can* accomplish this, but only if we make very few mistakes. Complications and accidents are sometimes unavoidable, but we cannot expect to maintain an appreciably lowered perinatal loss unless we consistently avoid those occasional fetal deaths due to "ill-defined and unknown cause."

The loss of a child during labor is depressingly tragic. In the past these experiences have sometimes left the obstetrician with a feeling of utter helplessness. We might as well have been blind, for we could not see what had happened. For days afterward no doubt we would have been willing, even anxious, to provide the careful and intelligent care necessary to detect an inadequate placenta before fetal distress is evident. Discussing the management of cases where fetal distress is suspected, Fitzgerald and McFarlane<sup>10</sup> have suggested that in the present state of our knowledge it is probably better to act on the basis of probability, than to accept a quota of "unavoidable" fetal deaths and permanently damaged children. They would agree, I am sure, that the obstetrician, though he cannot see, need not be helpless.

The placenta is only out of sight, not out of mind.

### References

1. Anderson, George W., and Nesbitt, Robert E. L., Jr.: Bull. Johns Hopkins Hosp. 97: 113, 1955.
2. Ballantyne, J. W.: J. Obst. & Gynaec. Brit. Emp. 2: 36, 1902.
3. Editorial: Brit. M. J. 2: 726, 1955.
4. Browne, F. J.: Brit. M. J. 2: 1142, 1955.
5. Calkins, L. A.: AM. J. OBST. & GYNEC. 56: 167, 1948; 68: 50, 1954.

6. Canon, R., Guilhem, and Mayer, M.: Bull. Féd. Soc. gynéc. et obst. 4: 145, 1952.
7. Clayton, S. G.: J. Obst. & Gynaec. Brit. Emp. 48: 450, 1941.
8. Clifford, Stuart H.: J. Pediat. 44: 1, 1954.
9. Eastman, Nicholson J.: AM. J. OBST. & GYNEC. 67: 701, 1954.
10. Fitzgerald, T. B., and McFarlane, C. N.: Brit. M. J. 2: 358, 1955.
11. Flexner, H., and Hellman, L.: AM. J. OBST. & GYNEC. 55: 469, 1948; 56: 861, 1948.
12. Gibberd, G. F.: New Zealand M. J. 51: 277, 1952.
13. Gibson, George: Brit. M. J. 2: 715, 1955.
14. Gold, E. M.: J. A. M. A. 159: 244, 1955.
15. Holmes, Rudolph: AM. J. OBST. & GYNEC. 56: 167, 1948.
16. Hughes, E. C., Van Ness, A. W., and Lloyd, C. W.: AM. J. OBST. & GYNEC. 59: 1292, 1950.
17. Kamperman, George A.: AM. J. OBST. & GYNEC. 56: 170, 1948.
18. Kellogg, Foster: Personal communication.
19. Kramer, H.: Brit. M. J. 2: 726, 1955.
20. Lund, Curtis J.: AM. J. OBST. & GYNEC. 40: 946, 1940.
21. Malpas, Percy: J. Obst. & Gynaec. Brit. Emp. 40: 1046, 1933.
22. Mills, W. G.: Brit. M. J. 2: 906, 1955.
23. Nesbitt, Robert E. L.: Obst. & Gynec. 8: 157, 1956.
24. Smith, Clement: Am. J. Dis. Child. 82: 171, 1951.
25. Smith, George V., and Smith, Olive W.: Obst. & Gynec. 4: 129, 1954.
26. Stallworthy, John: Brit. M. J. 2: 488, 1955.
27. Walker, James: J. Obst. & Gynaec. Brit. Emp. 61: 162, 1954.
28. Webster's New International Dictionary, second edition unabridged, Springfield, Mass., 1957, G. & C. Merriam Company, Publishers.
29. Whitehouse, D. B.: Brit. M. J. 2: 488, 1955.



## GROUP PREMARITAL COUNSELING\*

### A Follow-Up Study

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**D**ESPITE the tremendous advances in diagnosis and therapeutics which medicine has seen during this century, by far the greatest progress toward health has been achieved in the area of preventive medicine. In our specialty of obstetrics and gynecology we have kept apace in eliminating many of the organic perils connected with marriage, pregnancy, and childbirth, but until recently little has been done in regard to emotional hazards.

Nowhere are emotions more deeply and pervasively involved than in our area of medicine. Nowhere is it more medically advantageous that ignorance, and the fears so solidly rooted in ignorance, be eradicated. The role our specialty can and should play in dispelling ignorance in the matter of sexual adjustment in marriage is increasingly admitted. McCormick's<sup>1</sup> article in *Obstetrics and Gynecology*, Dickinson's<sup>2</sup> books, and Fishbein's<sup>3</sup> compilation of the work of 38 authors, all are indications of the growing recognition of our potential contribution in this matter. This can also be seen in the programing on the part of the American College of Obstetricians and Gynecologists.

If it is claimed that medical men can contribute significantly to this premarital education, it may be of some interest to discover what are some of the outcomes of such counseling in actual practice. This paper presents the results as indicated by a follow-up study of a portion of 746 couples who in the past six years had received group premarital counseling.

The group which provided the data to be presented participated in premarital education courses conducted by the Catholic Archdiocese of Indianapolis. These courses, offered exclusively to engaged couples, cover courtship, male and female psychology, practical economics, spirituality and canon law, and the medical aspects of marriage. Two one-hour lectures per night are given twice a week for a period of five weeks. A note from the local pastor attesting the engaged status of the couple is required for admission, but attendance is not compulsory.

The medical aspects of marriage, the lectures given by this author, and the subject of this paper, are covered in the last six lectures of the course. These six lectures may be briefly outlined as follows:

\*Presented at the Twenty-fourth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 4, 5, and 6, 1956.

Following the necessary introductory remarks the first hour is occupied by the playing of four records on sexual education of children covering:

1. How babies are born
2. Menstruation
3. Problems of young boys
4. The marriage union

These records, produced for the Christopher Movement by professional actors, are very thorough, accurate, and interesting. Actually they are intended to serve as a guide to parents in sexual education of their children, but they admirably serve our purpose in "breaking the ice" for the pre-marital group as regards terminology, and indirectly in demonstrating to the great majority of those present that their own early sexual instruction was inadequate. The second hour is devoted to anatomy and physiology of the female reproductive organs. Clay models and kodachrome slides are used as visual aids.

The third hour covers the anatomy and physiology of the male reproductive organs and sexual hygiene.

The fourth hour deals with pregnancy.

The fifth is concerned with marital relations, and here a very frank discussion, with nothing pertinent omitted, is presented. The last lecture covers the honeymoon and the early marital adjustment required upon the return to the humdrum everyday existence.

Question-and-answer periods are included as a part of each presentation and for better audience participation the couples are divided into separate groups for the last four lectures. This division of the group has been a controversial point, but since the more timid individuals are usually those in most need of the education it is felt that anything we can do to encourage their participation is justified.

Upon completion of the course the couples are presented with a formal certificate of completion. They are very proud of these certificates and several have been framed and hanging on the walls of their homes.

### Material

During a six-year period (1949-1955) 746 couples attended the lectures. Understandably the high residential mobility of a group of young married couples makes a comprehensive follow-up study quite difficult. For our study a group of 200 was traced through the telephone directory of the city of Indianapolis. The identification of the couple was verified through a telephone call before our questionnaires were mailed. Of the 200 questionnaires sent 118 had been returned at the time of our analysis. The wife was requested to fill out the anonymous questionnaire.

It is thoroughly understood that we are dealing with a selected group and therefore we wish to make no comparisons. First, the group is selected in so far as these young couples were serious enough about their marriage to give up voluntarily ten of their precious courtship evenings to receive instruction. Their marriages were more likely to succeed because they were that type of individuals. Second, the religion of the great majority of the group forbids remarriages after separation, and therefore makes it more necessary

for the first to succeed. Third, the method of selecting the group analyzed (the telephone book) tends to exclude any divorced or separated couples. These factors were fully recognized as likely to give a somewhat unbalanced report on the efficacy of premarital counseling, and hence a certain caution in applying these findings to other premarital counseling situations is quite in order.

### Findings

The average age of the girls at the time of instruction was 22.5 years with a range of 17 to 36 years. There were 21 below 20 years of age, 91 in the twenties, and 6 over thirty. The average length of time elapsed after taking the course and before marriage was 3.9 months with a spread of 0 to 18 months.

Of the 118 girls who replied, only 4 stated they did not enjoy marital relations and 9 had not achieved "complete satisfaction." It is surprising to note that one of those who stated she did *not* enjoy marital relations experienced "complete satisfaction" 90 per cent of the time and another 75 per cent of the time.

Of the 118 who answered there were 10 who did not know when they first achieved complete satisfaction.

	TIME TO COMPLETE SATISFACTION	CUMULATION
IMMEDIATE	17	(17) 15.7%
NOT IMMEDIATE BUT BEFORE ONE MONTH	25	(42) 38.6%
BETWEEN ONE MONTH AND SIX MONTHS	31	(73) 67.6%
BETWEEN SIX MONTHS AND ONE YEAR	13	(86) 79.0%
OVER ONE YEAR	13	(99) 91.1%
NEVER	9	(108) 100%

Fig. 1.

Fig. 1 demonstrates the answers given by the remaining 108. It shows that 17 achieved complete satisfaction almost immediately. There were 25 who achieved it within one month, 31 between one month and six months, 13 between six months and one year. Another 13 required more than a year, and 9 had never achieved complete satisfaction. The cumulation indicates that 73, or 67.6 per cent, achieved complete satisfaction within six months and 86, or approximately 80 per cent, within the first year.

There were 7 who stated that they had achieved complete satisfaction 100 per cent of the time, 78 over 50 per cent of the time, and 14 less than 50 per cent of the time. Interestingly enough, the 7 mentioned above who stated 100 per cent of the time were chiefly in the group of those who had been married the longest period of time.

The average incidence of marital relations was 7.5 times per month, with very little variation between the group married one year and that married seven years. The incidence varied from 2 to 20 times per month. Three

stated that they did not participate actively in marital relations. All 3 had been married over five years. One of them had never had complete satisfaction and another achieved it only one-third of the time.

Fifteen felt that they had some physical obstacle to marital relations and 10 consulted a doctor because of it. None required hymenotomy. Another 4 consulted a doctor because of emotional difficulties regarding sexual adjustment.

A few brief quotations from the remarks column will be presented in order to reflect the content of the lectures and also to show their effect on the marital adjustment of the couples.

1. *Case 56.*—"Yes, the lectures helped a great deal. The frank discussion of this subject alleviated the fear I had felt and helped me realize it was the most natural feeling in the world for married couples to display their love without feelings of disgust or guilt. I believe these lectures were of great value to my husband too. I shall always respect him for the gentleness, tenderness, and understanding he has shown me, particularly during that first critical year."

2. *Case 71.*—"I had always lived with a mother, aunt, and grandmother who had all been divorced when I was a baby so I had no idea what was expected of a wife in my capacity. These lectures helped me to understand many things and I am glad my marriage is a happy one."

3. *Case 88.*—"As in many homes I had no explanation of intercourse nor of organ function. It was always treated with secrecy and embarrassment. I believe we would have had a serious sexual adjustment to make if it had not been for these lectures because the condition existed in my husband's home also."

In reply to the question: "Did you ever become pregnant while carefully practicing rhythm?" 33 replied yes and 47 no. In reply to the same question regarding a temperature chart, 9 replied yes and 33 replied no.

As shown in Table I, there were 266 pregnancies including miscarriages. These are broken down into groups based on duration of marriage. Twenty-six were pregnant at the time the questionnaire was returned. The 24 miscarriages approximate the usual 8 to 10 per cent quoted in the literature.

TABLE I. PREGNANCIES

	YEARS MARRIED							TOTAL
	1	2	3	4	5	6	7	
Couples	10	12	20	14	22	31	9	118
Pregnancies	9	12	39	31	52	87	36	266
Pregnant now	4	1	9	3	2	4	3	26
Miscarriage	0	0	4	3	5	10	2	24
Living children	5	11	25	25	45	73	31	215
Infertile	-	1	2	2	2	4	0	11
Average no. of children (infertile excluded)	0.5	1.0	1.4	2.1	2.3	2.7	3.4	--

There were 11 cases of infertility, with the breakdown by years of marriage as shown. Only 3 of these persons stated they had consulted a doctor because of infertility. There were 215 living children and, excluding the infertile cases, it can be seen that the average number of children is about one for each two years married.

Table II shows the replies to the question, "Do you desire more children?" Ninety replied yes, 6 no, and 22 gave an equivocal answer such as "One more," "Want to wait awhile," "No, but if God sends them it will be OK." The 6 no answers came in the group married 5, 6 or 7 years. However, 4 with 4 or more children replied yes.



TABLE II. REPLIES TO QUESTION, "DO YOU DESIRE MORE CHILDREN?"

	YEARS MARRIED							TOTAL
	1	2	3	4	5	6	7	
Yes	7	11	15	12	16	24	5	90
No	0	0	0	0	3	1	2	6
Equivocal	3	1	5	2	3	6	2	22

The average weight gain in pregnancy was 22 pounds, and the average weight of the babies was 7 pounds 4 ounces. Only half, or 61 mothers, attempted to nurse the first child. The average length of the first labor was 12.5 hours; of the subsequent labors, 5.5 hours. It must be remembered that this is the patient's report and is probably longer than her doctor would have reported. Of the 218 labors the patients reported unconsciousness or amnesia in only 19.

The following quotation from the remarks column is presented because it is felt that it helps to show a connection between the lectures and labor.

*Case 40.*—"The lectures impressed me with the real importance of the physical side of marriage and gave me a better understanding of what to expect. They helped remove any feeling of guilt or shame. I personally benefited from knowing the true facts of childbirth for I enjoyed having each of my (3) babies."

#### Conclusions

1. Young people are anxious to have premarital instructions.
2. Group premarital counseling is a practical method of preparing couples adequately for marriage.
3. Thorough medical counseling as part of a general preparatory course for marriage is well received by both the engaged couples and the sponsoring organization.
4. When fear and ignorance are alleviated before marriage, women have shorter, easier labors and desire more children despite frequent pregnancies.
5. When fear and ignorance are alleviated women enjoy marital relations almost as universally as men.
6. Young married couples are happier as a result of premarital instruction and separations are undoubtedly reduced in number.
7. Young couples feel that a review of the course could well be given after marriage. This was brought out in the replies to the questionnaire and will be planned in the future.

#### References

1. McCormick, C. D.: *Obst. & Gynec.* 4: 355, 1954.
2. Dickinson, R. L.: *A Thousand Marriages*, ed. 3, Baltimore, 1953, Williams & Wilkins Company.
3. Fishbein, M.: *Successful Marriage*, ed. 2, Garden City, N. Y., 1955, Doubleday & Company, Inc.

#### Discussion

**DR. WILLIAM COOLEY, JR.,** Peoria, Ill.—The benefits of premarital examination, advice, and counsel bring a constantly increasing group of engaged couples to their physicians prior to the wedding day for assistance and guidance, particularly with reference to the physical and emotional aspects of marriage. Just as more and more young women seek the care of the trained obstetrician, also more young couples, particularly the female member of the pair, seek premarital instruction from the obstetrical specialist.

The professional demands upon the time of the busy obstetrician and gynecologist prevent his doing full justice to this challenge in each individual situation. Dr. Muller's suggestion of group premarital counseling provides an ideal means of more leisurely and detailed instruction.

As the author has suggested, the subjects from whom these statistics are drawn are a selected group, all members of a religious faith with very positive and disciplined beliefs regarding separation and divorce. These statistics, therefore, are not entirely suitable for comparison. However, the value of the group counseling is well demonstrated as a means of conserving the limited time of the busy obstetrician and still providing the benefit of his advice and counsel to the greatest number of engaged couples.

In our community of Peoria, Illinois, we have had no experience in premarital counseling on a group basis. We have, however, had considerable success with group prenatal instruction provided with the cooperation of the local Health Department, Medical Society, and the Y.W.C.A. The course consists of four afternoon classes for the expectant mother, followed by four evening classes for both the expectant mother and father, culminated by a tour of the maternity department of the hospital in which the mother expects to be confined. This includes visits to the labor, delivery, and postpartum sections. The nurses in charge give short talks of welcome and explanation. Patient response has been very gratifying, and labor room personnel are convinced that "graduates" of the prenatal course present themselves as much less apprehensive and more composed candidates for labor.

This program of group instruction has been so well received that the introduction of an additional course has been necessary. This second course consists of eight evening sessions to provide opportunity for group instruction for the expectant mother who continues to work during the early months of her pregnancy, and thus is unable to attend the daytime classes. Patients enrolled in these courses on a group basis have the definite advantage of eight hours of instruction which their attending physicians could not have provided to each as an individual.

DR. CHARLES E. GALLOWAY, Evanston, Ill.—It is quite evident that the sexual life of a female is not comparable in any way to the sexual life of a male, because very few of them derive satisfaction from their first contact, and they have to be educated up to that. One of these courses is the very way in which we will help women come into marriage with a little more enjoyment of their married life.

I cannot quite agree with the author when he says that a woman's sexual relations are as well developed or can be as well developed as a man's. In many instances they are better developed, as far as that is concerned, but those women are very, very exceptional.

When these lectures are being given, I think one of the things that should be explained to women is that the greater part of their sexual expression will be through reproduction and not through intercourse. A man has nothing whatever to compare with it, and they should look upon it as being something to achieve to grow into their sexual life, but the physical, chemical, anatomical, and all the other changes that come with pregnancy satisfy a woman's body, regardless of whether she thinks so in her mind or not.

DR. MULLER (Closing).—Dr. Cooley agrees that group premarital instruction is the answer. I did not make any calculations, but I could imagine that the number of hours required to give individual premarital instruction to this same number of people, and give it adequately, would be considerable.

I think Dr. Galloway forgot that I said "almost as universally as men." I do not think they will ever get to the 100 per cent appreciation that men have. I do not even think that can be our goal.

The 9 we had here at the bottom represent progress. Perhaps if we talked to these women again, after their marriage, after they have had some experience, after they know more about what they are talking about, I think we could reduce this number.

The reproductive angle that Dr. Galloway spoke of is most interesting. Since this is an emotional thing, since it is not completely a physical reaction, perhaps the reproductive angle does enter into it quite a bit.

**A PROCEDURE TO CORRECT PERSISTENT OCCIPUT POSTERIOR  
AND TRANSVERSE ARREST POSITIONS AND FACILITATE  
DELIVERY OF THE FETAL HEAD USING A SINGLE  
FORCEPS APPLICATION\***

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**D**URING my training and the early years of my private practice, the management of the persistent occiput posterior and transverse arrest positions of the fetal head was a real problem. I was taught to deliver the fetal head by the Scanzoni maneuver, by manual rotation, by the use of the Kielland forceps, or to deliver the head as a posterior.

The principal objections to the Scanzoni maneuver are the double application of forceps, and many times after rotation has been accomplished and the forceps have been removed for reapplication, one finds that the occiput has returned to its original posterior position. A clamp could be applied to the baby's scalp to hold the head in the anterior position while the forceps are being reapplied, but then a wound has been made in the scalp, so why do this if it is unnecessary? Also, the forceps ordinarily used in the Scanzoni procedure, the Simpson or Elliott, were not designed for rotation and should be used primarily for traction. When used as a rotator blade, they frequently cause cuts and tears in the cervix and vaginal walls.

To rotate a persistent occiput posterior manually is extremely difficult in most instances and, if the head has descended to occupy the lower pelvis, it must be displaced upward before rotation can be accomplished.

To rotate by use of the Kielland<sup>1</sup> procedure the anterior blade is introduced into the uterus, with the concavity of the cephalic curve looking upward, and then turned completely over to apply to the head. There is danger to the lower uterine segment and to the fetal head in accomplishing this part of the procedure.

To deliver a posterior as such is in most instances a difficult and damaging procedure because of the inability of the head to deflex and thus allow the smaller diameters to engage the pelvic outlet. This causes, at times, great and sometimes almost irreparable damage to the structures that form the pelvic outlet.

Because of the difficulties just enumerated in connection with the procedures mentioned, I spent the first five years of my practice experimenting

\*Presented at the Twenty-fourth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 4, 5, and 6, 1956.

with different forceps and different procedures and toying with the idea that there should be, and must be, an easier and less damaging procedure for the correction of persistent posterior and transverse arrest positions.

I have found the Piper<sup>2</sup> forceps to be most suitable for this procedure. The somewhat flattened pelvic curve, the long shank and depressed handles facilitate rotation with little compression of the fetal head, and, once rotation has been accomplished, delivery of the fetal head is easily done by slight horizontal traction in the direction of the handles, followed by deflection of the head in the normal manner. Thus the entire procedure of application of the forceps, rotation, and delivery of the head by traction can be accomplished with a single application of the forceps.

I have used this method since 1935. It is very easy and converts an almost formidable condition into a relatively simple one.

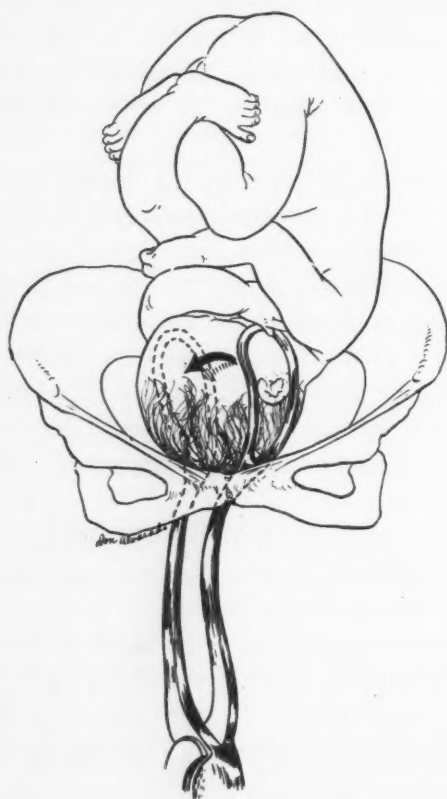


Fig. 1.



Fig. 2.

Fig. 1.—Correct cephalic application of forceps in left occiput posterior position.  
Fig. 2.—Correct cephalic application of forceps in right occiput posterior position.

It is unwise to attempt to deliver a head that is high up in the pelvis, or one that is unengaged, or where there is sufficient midplane disproportion to allow the head to become fixed with an incompletely dilated cervix, as this is a damaging procedure to both mother and baby. When the head descends to the pelvic floor where rotation should normally take place, and does not, it becomes a simple procedure to rotate the head and extract the baby.



The procedure that I have used is as follows:

When the head is in an occiput posterior position, left or right, the left blade of the forceps is always introduced first, followed by the insertion of the right blade and the handles are locked; thus a correct cephalic application is obtained (Figs. 1 and 2).

To apply the forceps in a left occiput posterior position, the operator stands just inside the right thigh and faces obliquely to the patient's left side. The left blade of the forceps is introduced into the hollow of the sacrum and is moved counterclockwise until it is applied to the right side of the fetal head. The right blade of the forceps is next introduced into the hollow of the sacrum in apposition to the left side of the fetal head. The forceps handles are then locked, and the pelvic curve is toward the face of the fetal head.

In the right occiput posterior position, the operator stands just inside the left thigh and faces obliquely to the patient's right side. The left blade of the forceps is introduced into the hollow of the sacrum and is applied immediately to the right side of the fetal head. The right forceps blade is next introduced into the right side of the hollow of the sacrum, behind the occiput, and is rotated clockwise until it is applied to the left side of the fetal head. The forceps handles are then locked, and the pelvic curve is toward the face of the fetal head.

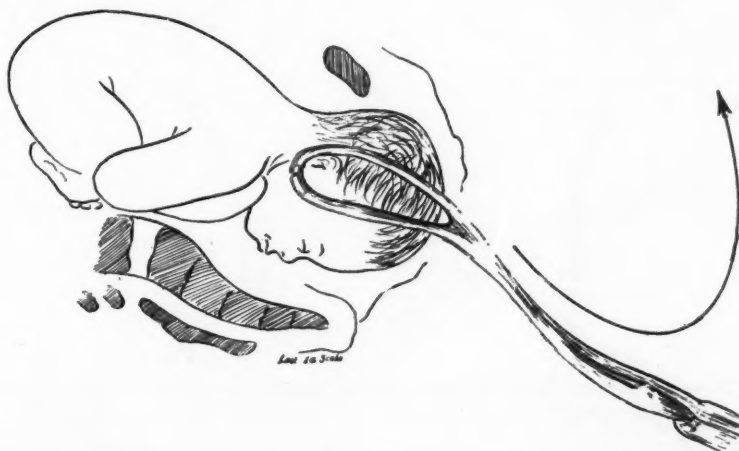


Fig. 3.—Lateral view shows correct cephalic application of forceps with pelvic curve of the forceps "upside down" after rotation from a posterior to an anterior position.

The forceps handles are then rotated through a small arc, thereby turning the occiput to an anterior position. In a left occipitoposterior, the rotation of the fetal head to an anterior position is counterclockwise, while the rotation in a right occipitoposterior position to anterior is clockwise. In either instance the arc of rotation is 135 degrees and the pelvic curve of the forceps, after rotation, is actually "upside down" (Fig. 3). After complete rotation to anterior has been accomplished, it is usually easy to deliver the fetal head with slight depressed traction, in the direction of the handles, until the occiput crowns at the introitus, and then by allowing the forceps to follow the normal deflection of the head (Fig. 7). I prefer, therefore, to complete rotation of the occiput before any traction is made, as this permits the smaller diameters of the fetal skull to engage the pelvic outlet, and thus very little traction is usually required for delivery of the head.

When the head is in transverse arrest, whether the occiput is left or right, the left blade is inserted first followed by insertion of the right blade and sliding it into position to obtain a correct cephalic application (Figs. 4 and 5).

In the left occiput transverse position the left forceps blade is slipped into the hollow of the sacrum and is applied immediately to the left side of the fetal head. The right forceps blade is next inserted in the right side of the vagina

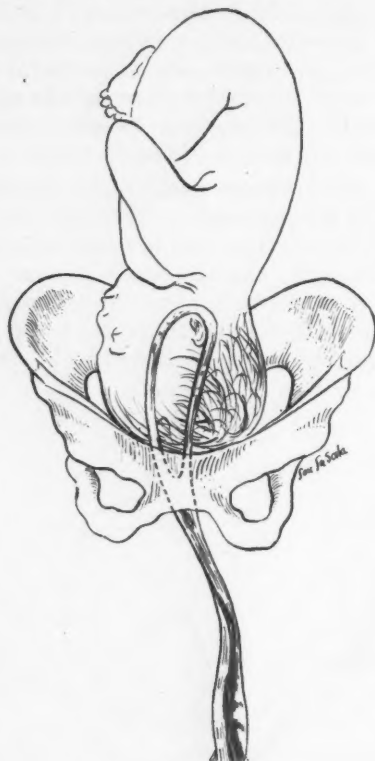


Fig. 4.

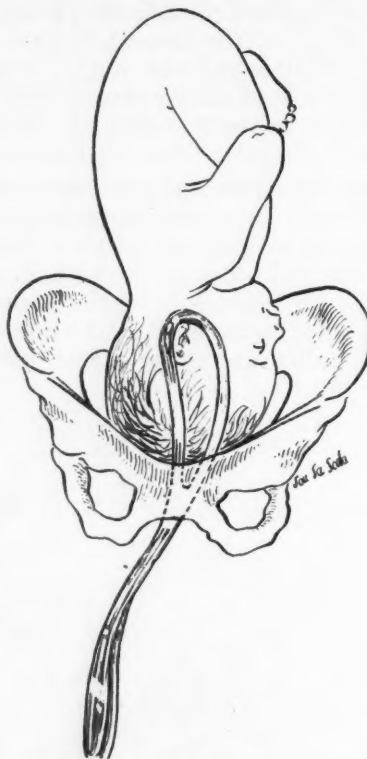


Fig. 5.

Fig. 4.—Correct application of forceps in left occiput transverse position.  
Fig. 5.—Correct application of forceps in right occiput transverse position.

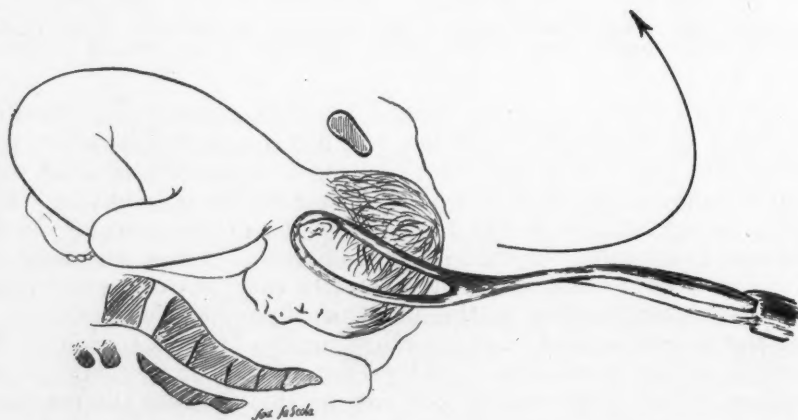


Fig. 6.—Lateral view shows correct cephalic application of forceps with pelvic curve of the forceps "upright" after rotation from a transverse to an anterior position.

and pelvis and is moved clockwise over the forehead to the frontoparietal region and anteriorly in the pelvis and is applied to the right side of the fetal head. The forceps handles are then locked, and the pelvic curve is toward the fetal occiput or to the patient's left (Fig. 4).

In the right occiput transverse position, the left forceps blade is inserted into the hollow of the sacrum and is moved counterclockwise over the forehead to the frontoparietal region and anteriorly in the pelvis and is applied to the left side of the fetal head. The right forceps blade is next inserted into the hollow of the sacrum and is applied directly to the right side of the fetal head. The forceps handles are then locked and the pelvic curve is toward the fetal occiput, or to the patient's right (Fig. 5).

When rotation occurs from transverse to an anterior position, from either left or right, the arc of rotation is 90 degrees and the pelvic curve of the forceps, after rotation has been completed, is "upright" (Fig. 6). Delivery of the fetal head is usually easily accomplished by slight traction horizontally in the direction of the handles, until the occiput crowns, and by allowing the forceps to follow normal deflection of the head in the normal manner (Fig. 7).

At times the head may be difficult to rotate and this may be facilitated by making slight pressure upward on the head with the hand and forceps followed by rotation.

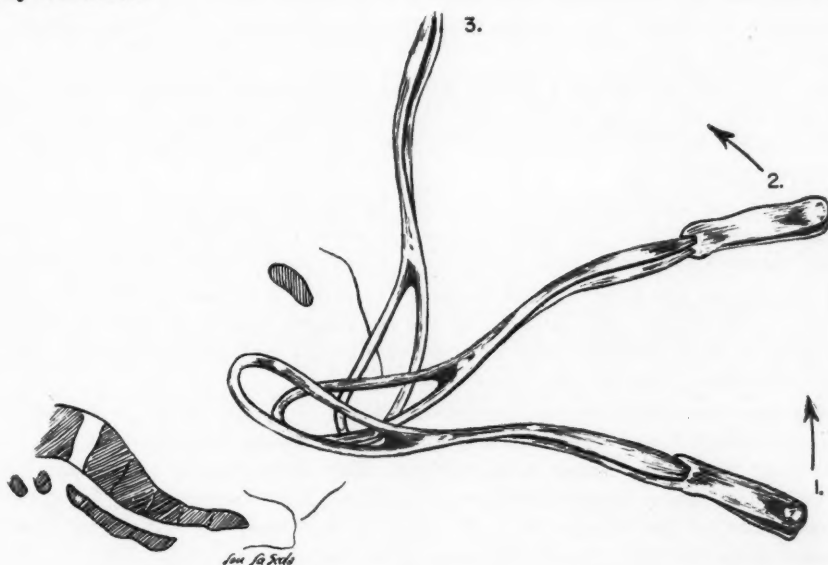


Fig. 7.—Shows position of forceps during deflection of the head.

Sufficient anesthesia is used to permit episiotomy, the forceps procedure, and repair of the episiotomy. This actually shortens the second stage.

In my earlier years with this procedure, after rotation had been accomplished, I would at times remove the forceps and allow the forces of labor to expel the fetus spontaneously. In some instances the forceps would have to be reapplied and extraction accomplished. During the past fifteen years I have completed the delivery with the single application of the forceps and have found this to be most satisfactory. Occasionally slight abdominal pressure will facilitate delivery. In less than 5 per cent of persistent occiput posterior and transverse arrest positions has it been necessary, after rotation was accomplished with the Piper forceps, to replace them and complete the delivery with a traction forceps.

The Piper forceps were originally designed to facilitate the delivery of the aftercoming head in breech extraction. In addition to using them as just described, I have successfully used them to rotate and extract the aftercoming head of the breech in the platypelloid type of pelvis.

### Summary

Persistent occiput posterior positions and deep transverse arrests can be easily corrected and delivery can be accomplished with a single application of Piper forceps when used in the manner described.

The procedure is relatively simple when correctly timed and when properly used.

### References

1. Kielland, Chr.: *Monatsschr. Geburtsh. u. Gynäk.* 43: 1, 1916.
2. Piper, Edmund: *J. A. M. A.* 92: 217, 1929.

### Discussion

DR. JAMES H. BEATON, Grand Rapids, Mich.—Any forceps procedure which assures the safe delivery of an arrested fetal head is a valuable contribution to clinical obstetrics. Our literature is replete with various forceps and maneuvers; so we must assume "the perfect one is yet to come."

Dr. Smith has presented a unique method, which seems basically sound. Apparently it has been most successful or he would have discarded it in the past twenty years. His frequent use of the words "easy," "simple," and "less damaging" signify a doctor who has respect for fragile tissues.

In using the Piper forceps for rotation, he displays originality and fortitude. Most obstetricians insist that a Kjelland forceps is a must, for skillful rotation. I have always felt that the type of forceps was insignificant, as compared to the operator's ability.

I have never tried Dr. Smith's method; therefore I am not justified in criticizing it adversely. Also, I am a firm believer in the old adage, "you can't criticize success." For the purpose of discussion, I would like to describe the method I learned at Cook County Hospital seventeen years ago and have used ever since.

In a deep transverse arrest the anterior blade is applied first, by wandering it over the smooth occiput for an ideal cephalic application. To do this, one must "back the blade into position" with the inferior edge leading. This all-important trick cannot be clearly described, but is easily demonstrated on a manikin. The posterior blade is slipped directly into the hollow of the sacrum until it comes to rest over the ear. This ideal cephalic application gives the least chance for a tentorial tear.

Now the forceps are locked and the head is flexed slightly for easy rotation. At this point, one must have a clear understanding of how much pelvic curve there is in his forceps, so that he may compensate by sweeping the handles through a proper arc. If the head does not rotate easily, your technique is faulty or your judgment for delivery was wrong. Do not blame the forceps, blame yourself.

After rotation, the head should be delivered by repeated applications of gentle traction. If brute force is required, you have most likely "jumped" this case too soon or relative disproportion is present. Do not forget that you can always take the forceps off, admit your error, and either wait or do a cesarean section.

For a persistent posterior, I have always used the modified Scanzoni with the DeLee-Simpson forceps. The secret of success lies in adequate flexion and rotation of the handles through a proper arc, to avoid laceration. The easy ones are easy, irrespective of maneuver or forceps model. The difficult ones are difficult, in spite of tricks or fancy blades. I think this is the reason we have so many forceps and new maneuvers.



I work in a general hospital where we preach ultraconservatism. In a series of 25,243 deliveries over a nine-year period, we have the following to report: spontaneous delivery 84 per cent, forceps 13 per cent, forceps rotation 1 per cent, midforceps 0.3 per cent, cesarean section 1.4 per cent. These figures include a substantial number of forceps operations for teaching purposes.

In summary, let us remember that forceps rotation is operative obstetrics. One must have a real indication for interference before trying to improve upon nature. I believe Dr. Smith has given us a logical method for those few cases which require interference.

DR. HUGH G. HAMILTON, Kansas City, Mo.—I think Dr. Beaton's point is very well taken about the multiplicity of forceps. Years ago, Dr. Piper said that the reason he devised nine different forceps was to make up for his own lack of manual dexterity.

In the application of forceps in abnormal positions, I do not think it makes a bit of difference what forceps you use; the proper and important thing is that you must make a cephalic application. Then, if you push the head back up a centimeter or so, rotation usually becomes quite easy.

I do not understand why, when Dr. Smith is making an application—regardless of whether it is transverse or posterior—he does not make a correct cephalic application and then, when he completes his rotation, he can have a correct pelvic application instead of making the delivery of the posterior with a correct cephalic and incorrect pelvic application.

DR. SMITH (Closing).—Dr. Beaton displayed a procedure that he has used for a number of years, which brings up the point that, irrespective of all the forceps that have been devised for deliveries, one should still develop the method that is most suitable to himself and which is most properly used. I believe that one is less likely to cause damage to the soft parts with the Piper forceps.

Dr. Hamilton wanted to know why I used the Piper forceps. I suppose it is simply because I have used them so much, and during my experimenting with different forceps, it seemed to me that these forceps were most suitable. I think the very making of the forceps, lends itself quite well to this application which I described.

Dr. Hamilton also asked why I did not make a correct cephalic application in an occiput posterior. That can be done. It just so happens, though, that I have found in the occiput posterior that you can make the application and rotate it around so easily and deliver the fetus with a single application that I have not tried it that way. However, I see no reason why it could not be done.

## OBSERVATIONS ON THE POLYCYSTIC OVARY SYNDROME\*

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IN 1935, Stein and Leventhal<sup>1</sup> called attention to a syndrome characterized by amenorrhea, occasionally menometrorrhagia, sterility, and hirsutism. The pathological findings were large, pale, polycystic ovaries with thickened capsules. Therapeutically, it was found that with adequate wedge resection of both ovaries, fertility and regular menstrual periods could be achieved in many instances. Subsequently authors<sup>2, 3, 4</sup> have confirmed this syndrome and have emphasized the value of ovarian surgery on selected patients.

The diagnosis and proper selection of patients who will respond favorably to ovarian resection seem most important. The history, pelvic findings, and gynecography have been the principal diagnostic aids available. Unless one is constantly conscious of this syndrome it is easy to overlook such patients. In this clinic, the syndrome was not diagnosed until 1952. At that time the first patient was treated by bilateral ovarian resection but a favorable response was not obtained. Two years later, since menstruation had occurred only once since operation, it was suggested that a course of gonadotrophic extract might produce ovulation. This medication was started and within a few days the patient complained of severe abdominal pain and fullness. Pelvic examination disclosed one ovary to be 15 by 10 cm. and the opposite ovary was slightly smaller. Fortunately, this ovarian enlargement regressed in two weeks' time. This event posed the question whether this unusual response was typical for patients with polycystic ovaries. In this paper two new aids will be presented; one, the response of polycystic ovaries to pituitary extracts, follicle-stimulating hormone (FSH), and, second, a biological determination of luteinizing hormone (LH).

### Material

Two gonadotrophic pituitary extracts were available for use, one produced by Armour and Company and the other by Parke, Davis & Company.† The Armour FSH was given intramuscularly in daily doses of 25 units for 6 days and the Parke, Davis FSH was given in doses of 100 units daily for 6 days.

\*Presented at the Twenty-fourth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 4, 5, and 6, 1956.

†The Armour FSH is extracted from hog pituitary powder after partial digestion with pancreatin. Parke, Davis & Company FSH is obtained from either hog or sheep pituitary by fractional precipitation. Each preparation is assayed biologically in immature female rats which are also given augmenting doses of human chorionic gonadotrophin (Parke, Davis 12.5 I.U. per test rat and Armour 20 I.U. per test rat). The Armour assays are based on comparisons with their standard FSH reference powder. The Parke, Davis assays define a rat unit as that amount which doubles the rat ovarian weight. Since the manner of preparation and the bioassays differ, there has been no effort to equate the extracts in terms of labeled unitage.

These follicle-stimulating hormone preparations were given to 13 patients suspected of having polycystic ovaries and 36 other patients as controls. Three types of control patients were selected: (1) young patients, aged 18 to 30 years, brought to the hospital for Eugenics Board sterilization; (2) obstetrical patients admitted for therapeutic abortion or repeat cesarean section; (3) gynecological patients with uncomplicated myomas or with severe functional uterine bleeding but with normal ovarian findings.

Each Stein-Leventhal patient was studied as completely as possible: vaginal smears, endometrial biopsies, protein-bound iodine, 17-ketosteroid and gonadotrophin assays were obtained. The gonadotrophin determinations were qualitative rather than quantitative in the estimation of LH. Kaolin was added to the 24 hour urine specimens to absorb the gonadotrophins.<sup>5</sup> The final extracts were injected into immature rats and the ovarian weight and condition of the uterus noted at autopsy. The ovaries were fixed in Bouin's fluid and histological sections were prepared. If there was a pronounced hyperemia and hypertrophy of the theca interna with relatively little stimulation of the granulosa, the extract was judged to be primarily LH in character. If there were many cystic follicles and pronounced stimulation of the granulosa, the effect was judged as primarily due to FSH.



Fig. 1.—F. H. Laparotomy after injections of FSH. Ovary 9 by 6 by 6 cm.

### Results

The results are summarized in Table I. Of the 13 patients with polycystic ovaries, all but one responded to FSH with marked ovarian enlargement. The ovaries measured 6 by 5 cm. and larger. Both ovaries were enlarged (Fig. 1) and although the degree of enlargement varied, the normal shape was maintained. The ovaries had a whitish-gray appearance. Gray areas representing cysts bulged through the tunica. The usual ovarian wrinkling was absent. Wedge resections were done on 4 patients while the ovaries were still enlarged. Grossly the cortex was composed of many follicles, 0.5 to 1 cm. in diameter (Figs. 2 and 3). The ovarian stroma was very edematous. Microscopically there was a thickened tunica albuginea and beneath this were multiple cysts in various phases of development, and lined by a thick layer of granulosa cells. A few primordial follicles were seen, but no corpora albicantia.

TABLE I. OVARIAN RESPONSE TO ADMINISTRATION OF FSH

	OVARIAN RESPONSE TO ARMOUR FSH			OVARIAN RESPONSE TO PARKE, DAVIS FSH		
	NONE 3 BY 2 CM.	SLIGHT 4 BY 2 CM.	MARKED 6 BY 5 CM.	NONE 3 BY 2 CM.	SLIGHT 4 BY 2 CM.	MARKED 6 BY 5 CM.
Eugenics Board sterilization	6	3	0	4	2	0
Myomas or metrorrhagia	4	0	0	7	0	0
Therapeutic abortions, cesarean sections	6	1	1	2	0	0
Polycystic ovaries	0	1	5	0	0	7
Total	16	5	6	13	2	7



Fig. 2.—F. H. Right ovary resected and sutured. Wedge being resected from left ovary.



Fig. 3.—Wedge resected from ovary of N. S. after course of FSH injections. Cystic follicles 0.5 to 1.0 cm. in diameter.



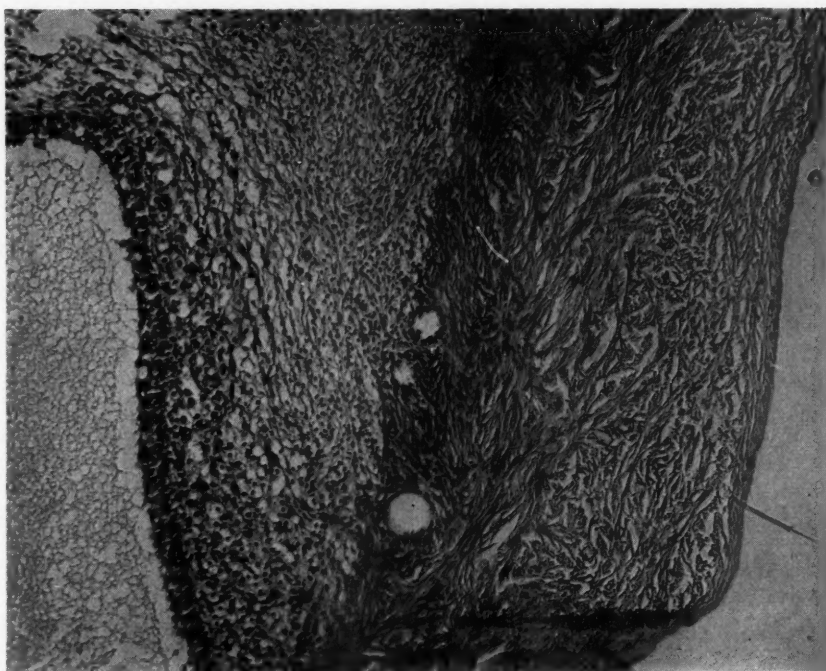


Fig. 4.—Thick tunica albuginea of Stein-Leventhal syndrome. Note also hypertrophied thecal tissues and thin granulosa. Patient F. R. Wedge biopsy two years prior to FSH.

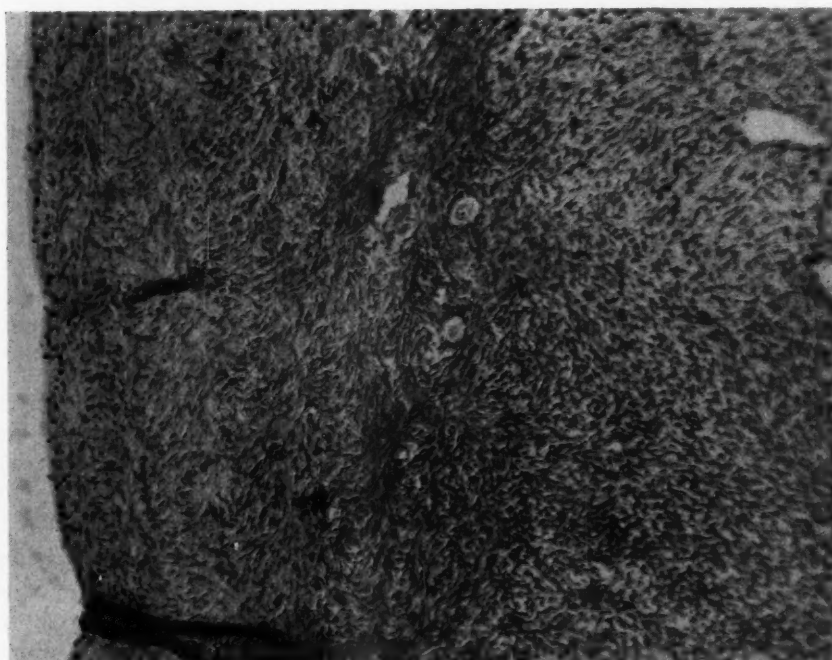


Fig. 5.—Ovary of Stein-Leventhal syndrome after treatment with FSH. Tunica still thickened even after ovary had enlarged to 9 by 6 by 6 cm. See Figs. 1 and 2.

TABLE II. THIRTEEN CASES OF POLYCYSTIC OVARIES

NAME	MENO- MET- ROR- RHAGIA	AMEN- ORRHEA	STERILITY (DURA- TION IN YEARS)	BODY BUILD	HIR- SUTISM	INITIAL SIZE OF OVARIES	PROTEIN- BOUND IODINE	17- KETO- STEROIDS	LH	ENDOMETRIAL BIOPSY	SIZE OF OVARIES AFTER FSH (CM.)	OPERA- TION	MEN- STRUAL PERIODS	PREG- NANCY
N. W.			2	Stocky	2+	1+	8.9	15	+	Proliferative	6 x 3	Yes	Regular	Too soon
N. S.		x	2	Stocky	0	0	3.5	8	+	Proliferative	8 x 6	Yes	Regular	Yes
M. S.		x	2	Thin	0	1+	6.0	12	+	Proliferative	7 x 5	Yes	Too soon	Too soon
E. R.		x	7	Thin	1+	1+	—	12	+	Atrophic	10 x 10	Yes	Too soon	Too soon
F. R.	x	x	6	Stocky	2+	2+	4.0	7	Not done	Hyperplastic	10 x 15	Yes	Irregular	Yes
T. P.	x	x	3	Thin	0	1+	4.3	8	Not done	Atrophic	10 x 6	Yes	Regular	Too soon
J. M.		x	2	Thin	0	1+	—	15	+	Secretory	8 x 5	Yes	Too soon	Yes
F. H.	Anovulatory cycles	x	7	Stocky	2+	0	4.3	12	+	Proliferative	9 x 6	Yes	Regular	Yes
M. G.		x	3	Thin	0	0	4.1	15	+	Atrophic	6 x 4			
L. G.	x	x	3	Thin	0	1+	—	9	+	Proliferative	8 x 5	Yes	Regular	
B. L.		x	2	Thin	0	1+	4.2	7	+	—	8 x 5	Yes	Regular	
K. H.		x	10	Thin	1+	1+	—	8	None	—	6 x 3	Yes	Regular	
B. O.	x	x	2	Thin	1+	1+	—	13	+	—	8 x 5			

The ovarian response in the control patients was very different. There were 15 court-ordered sterilizations and 10 of these patients showed no visible change, while 5 showed slight ovarian enlargement due to 2 to 4 cystic follicles. Eleven patients with gynecological problems showed no ovarian enlargement after a course of FSH injections. Of 10 pregnant or parturient patients treated, 8 showed no enlargement, one a slight change, and one a marked enlargement.

Thus, of 36 control patients only one showed a response comparable to those with polycystic ovaries, of whom 11 out of 12 had a marked ovarian response. Figs. 4, 5, and 6 show histological sections of treated and untreated ovaries. There is no appreciable thinning of the tunica despite the tremendous enlargement of the treated Stein-Leventhal ovary.

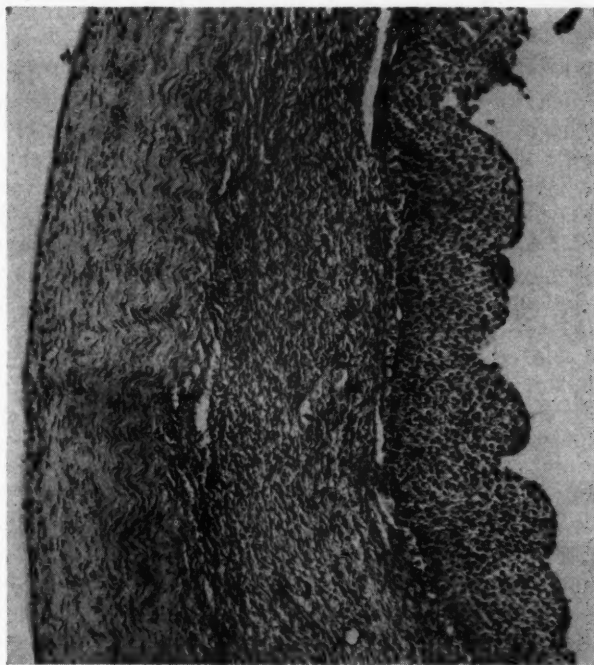


Fig. 6.—Control patient 8 days post partum at beginning of FSH treatment. Normal tunica and marked stimulation of granulosa. Ovaries 6 by 5 by 3 cm. This was the greatest ovarian response seen in a control patient.

The only difference in response to the two extracts was in patients with polycystic ovaries. When the Armour extract was given the ovaries enlarged during the 6 day injection interval. With the Parke, Davis extract the ovarian enlargement was not palpable until 4 to 5 days after cessation of the injections.

The first 2 Stein-Leventhal cases were not studied for LH gonadotrophin excretion; but in 11 other patients, LH was elevated in 10 instances. This seems to be a consistent finding and of definite diagnostic value. The 17-ketosteroids were slightly elevated in 7 patients; these elevations were not correlated to the hirsutism.

During FSH injections, the 17-ketosteroid excretion became double that of the pretreatment values in 3 patients (T. P., N. S., and E. R.) but in the

rest there was no significant change. In 2 (T. P. and N. S.) dehydroisoandrosterone (blue chromogen) became evident at this time. The blue chromogen also was noted again during the subsequent pregnancy in T. P. These observations suggest there may be an adrenal component in an occasional patient.

### Comment

The principal symptoms of this syndrome have been listed as amenorrhea or menometrorrhagia, sterility, hirsutism, and occasionally pain. The cases studied show comparable findings (Table II). It appears that perhaps the amenorrhea is the final phase of menstrual irregularity. While amenorrhea was a most consistent complaint, 6 out of 13 patients had had fairly recent intervals of irregular menstruation.

Sterility was a most consistent finding. Hirsutism was noted in 6 out of 13 patients. Body build seemed unimportant. Only 2 patients had significant ovarian enlargement at the time of initial examination, 8 showed slight enlargement, and in 3 cases the ovaries were felt to be of normal size.

A fairly typical menstrual history in many of our patients would be as follows: Menarche at the age of 11 to 13, with periods fairly regular for the first 2 or 3 years. Then the periods became irregular with episodes of prolonged bleeding. Gradually the periods became even more irregular with intervals of 2 to 4 months of amenorrhea. By the time the patient had reached the age of 21 or 22 she had married and had not become pregnant. The menstrual periods now were scant and infrequent, coming every 4 to 6 months. Eventually the patient became completely amenorrheic. Thus, there seems to be a long period of menstrual irregularity preceding the amenorrhea. Shippel<sup>6</sup> has correlated the progressive menstrual irregularity with the progressive accentuation of thecal tissue in the ovary. It is interesting to note that one patient in this series was menstruating very regularly but had ovulated only once or twice in a three-year period.

CASE OF F. H.—The patient, aged 25 years, was first seen in 1950 because of sterility of five years' duration. On three occasions she had gone 10 days beyond a period and had wondered if she had aborted. Physical examination showed a slightly obese woman with a moderate amount of hair on her face and upper lip. The physical and pelvic findings were normal and the ovaries were not enlarged. The tubes were patent and the husband's sperm count was normal. Because of a basal metabolic rate of minus 11, she was placed on thyroid therapy. During a three-year interval daily temperature graphs were kept and ovulation occurred only once or twice. Because the 17-ketosteroids were slightly elevated a course of oral cortisone was given but had no effect. Other attempts at therapy consisted of stilbestrol in the first part of the menstrual cycle, and also a course of Synapoidin. In 1955, a urinary gonadotrophin determination showed the presence of LH; later FSH was given with marked ovarian enlargement. A wedge resection of the ovaries was performed. Following this procedure there were three ovulatory periods followed by conception.

Ingersoll and McDermott<sup>3</sup> determined the excretion of gonadotrophic hormone in 12 cases of the Stein-Leventhal syndrome. By their technique the excretion of follicle-stimulating hormone (FSH) was judged within normal limits. Since they were unable to test for luteinizing hormone (LH) at that time they suggested that "possibly this pathological picture is due to excessive LH. . ." They noted the hypertrophy and luteinization of the theca interna in the patient's ovaries as described earlier by Robinson<sup>7</sup> and also by Stein and Cohen.<sup>8</sup> Plate<sup>9</sup> and Shippel<sup>6</sup> considered the syndrome as synonymous with ovarian hyperthecosis. Plate assumed the thecal changes were



evidence of excessive LH. This assumption is in accord with recent evidence that LH acts primarily on the theca while FSH acts primarily on the granulosa.<sup>10</sup>

Using the histological response of the immature rat ovary it was possible to demonstrate an excess of LH in 10 of 11 patients with polycystic ovaries. The presence of LH in this syndrome also had been demonstrated by another assay technique, namely, the response of the ventral prostate of the hypophysectomized male rat.<sup>11</sup> The probability that LH would give rise to vesicular follicles has rarely been considered. Lane,<sup>12</sup> however, presented evidence that LH was the factor responsible for the formation of the antrum in the Graafian follicles of rats.

The fact that polycystic ovaries respond so readily to FSH indicates that many of the vesicular follicles are in a state of stasis rather than one of cystic degeneration or atresia. Each of the static follicles responds by a rapid proliferation of the granulosa and accumulation of fluid. The response of these static follicles to FSH could be interpreted as proof of a deficiency of FSH. In the normal ovary there are usually only 3 or 4 vesicular follicles capable of responding to administered FSH so the response is limited.

These findings and interpretations are in accord with the studies of Davis and Hellbaum.<sup>13</sup> They administered fractionated pituitary extract (FSH) followed by one or 2 injections of unfractionated extract (FSH and LH) to a group of normal women and found that only 2 developed large ovaries and 5 had a slight response. Unfortunately, none of their patients were given the FSH extract only, so their findings are not strictly comparable to those of the present series. However, when they gave FSH and LH for as long as 10 or 12 days, 6 of 17 patients did develop large ovaries.

Sommers and Wadman<sup>14</sup> recently postulated FSH as the cause of polycystic ovaries. They apparently overlooked the fact that Davis and Hellbaum found FSH (fractionated extract) less effective than FSH plus LH (unfractionated extract) in causing ovarian enlargement. They also must have discounted the normal values for FSH found by Ingersoll and McDermott. Two patients with amenorrhea and infertility were found to excrete FSH type of gonadotrophin. They were given FSH for 6 days without any palpable ovarian enlargement. Thus it seems probable that FSH is not an etiological factor in polycystic ovaries.

The rapid and marked response of the polycystic ovaries is so characteristic that it seems the use of FSH offers a new diagnostic test. The stimulated follicles rapidly undergo atresia so the ovaries quickly regress in size after cessation of treatment. It had been hoped that this atresia would clear the ovaries of the static follicles and permit normal cycles to occur. However, most of the patients have had only one menstrual period after the cessation of treatment and 4 patients have been subjected to wedge resection, one to 6 months after the FSH stimulation. One of the patients (E. R.) had such a marked response to FSH that her ovaries were palpable as high as the umbilicus. On pelvic examination one month later, it was felt that the ovaries were only slightly greater than normal size. At laparotomy the next day, however, the ovaries were found to be 7 by 5 by 1 cm. in size. A number of follicles 3 to 4 mm. in diameter were found in the resected wedge. Another patient (J. M.) had similar findings at laparotomy. The flattened shape of these ovaries suggests the possibility that they could enlarge considerably without stretching or thinning of the tunica.

These observations do not indicate whether the pituitary or the ovary is primarily at fault in this syndrome. The consistent finding of LH does, however, offer the opportunity to determine whether ovarian hormones will alter this unilateral activity of the pituitary.

### Summary

Thirteen patients suspected of having the polycystic ovary syndrome were given a course of injections of FSH. All but one responded by a rapid and marked increase in size of the ovaries due to the formation of many cystic follicles. The ovaries rapidly regressed back to normal size within 2 weeks.

Thirty-six control patients were given a course of injections of FSH and only one showed an ovarian response comparable to that in the 12 patients with the polycystic ovary syndrome. Usually only 2 to 4 follicles exhibited a cystic change as evidence of stimulation.

Urinary gonadotrophin was checked in 11 of the patients with the Stein-Leventhal syndrome and in 10 instances it was found to be of the LH type, the others being entirely negative.

It is proposed that urinary assay for LH and a course of FSH injections are diagnostic aids in suspected cases of the polycystic ovary (Stein-Leventhal) syndrome.

### References

1. Stein, I. F., and Leventhal, M. L.: *AM. J. OBST. & GYNEC.* 29: 181, 1935.
2. Stein, I. F.: *AM. J. OBST. & GYNEC.* 50: 385, 1945.
3. Ingersoll, F. M., and McDermott, W. V.: *AM. J. OBST. & GYNEC.* 60: 117, 1950.
4. Buxton, C. L., and Van de Wiele, R.: *New England J. Med.* 251: 293, 1954.
5. Bradbury, J. T., Brown, E. S., and Brown, W. E.: *Proc. Soc. Exper. Biol. & Med.* 71: 228, 1949.
6. Shippel, S.: *J. Obst. & Gynaec. Brit. Emp.* 62: 321, 1955.
7. Robinson, M. R.: *AM. J. OBST. & GYNEC.* 30: 18, 1935.
8. Stein, I. F., and Cohen, W.: *AM. J. OBST. & GYNEC.* 38: 465, 1939.
9. Plate, W. P.: *Acta Endocrinol.* 8: 17, 1951.
10. Gaarenstroom, J. H., and de Jongh, S. E.: *Contribution to the Knowledge of Influences of Gonadotrophic and Sex Hormones on the Gonads of Rats, Monographs of Research in Holland, New York, 1946, Elsevier Publishing Co., Inc.*
11. MacArthur, J.: Personal communication.
12. Lane, C. E.: *Anat. Rec.* 61: 141, 1935.
13. Davis, M. E., and Hellbaum, A. A.: *J. Clin. Endocrinol.* 4: 400, 1944.
14. Sommers, S. C., and Wadman, P. J.: *AM. J. OBST. & GYNEC.* 72: 160, 1956.

### Discussion

DR. IRVING F. STEIN, SR., Chicago, Ill.—The authors are to be complimented for their careful scientific study on the etiology of the polycystic ovary syndrome. To date, the etiology is unknown and we have repeatedly claimed that the condition is endocrine in origin; we feel that the authors have made a sincere effort in this direction. In the course of their work, they have evolved what they consider a good test for bilateral polycystic ovaries. Such a test may be employed in the institutions which are equipped to carry out such laboratory procedures. Work of this type is to be commended inasmuch as it will serve to stimulate interest in the investigative aspects of this disturbance.

As one who holds a vested interest in the Stein-Leventhal syndrome, however, I cannot help but wonder at what are to me rather glaring omissions. The syndrome is a fairly uncommon one; therefore, I do not quarrel with observations made on a comparatively small number of cases. But, in this presentation, the authors discuss the appearance of

the ovaries and fail to state the method of observation. Were the ovaries visualized by pneumoroentgenography, culdoscopy, by colpotomy, or at laparotomy? It appears that these 13 cases were diagnosed on what I consider to be a presumptive basis only. History, physical findings, 17-ketosteroid determinations are not enough—and exploratory laparotomy is too much.

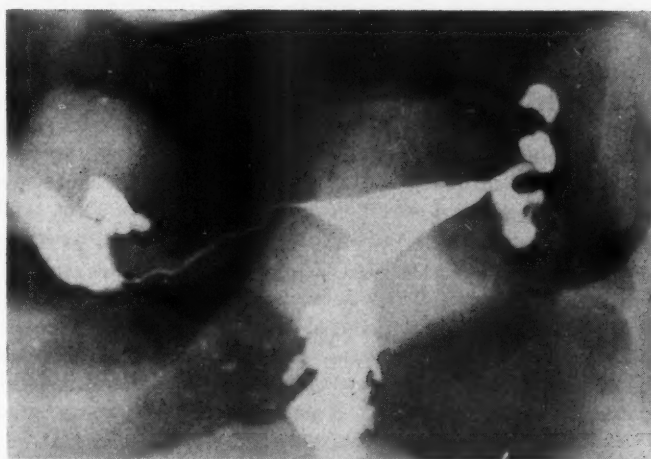


Fig. 1.—Polycystic ovaries demonstrated by pneumoroentgenography.

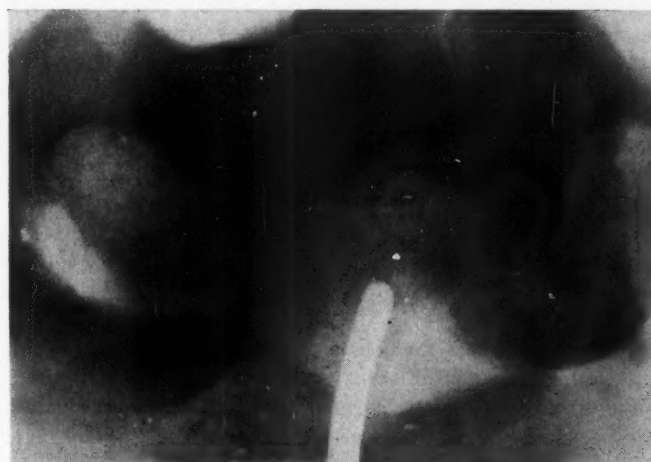


Fig. 2.—Polycystic ovaries demonstrated by complete gynecography.

We have found through more than a quarter of a century of observation that mistakes in diagnosis are made in a large number of cases unless visual diagnostic techniques are employed. We have three such methods in our diagnostic armamentarium which will confirm or negate a presumptive diagnosis. In the series reported on today, the authors state that only 2 of the 13 cases labeled bilateral polycystic ovaries showed significant enlargement by palpation. In my series of almost 100 cases, only 50 per cent of the ovaries could be palpated or said to be unilaterally or bilaterally enlarged on the basis of the bimanual examination alone. Diagnosis was established with the aid of pneumoroentgenography; in no case did we depend upon the exploratory laparotomy. We believe this means entirely unwarranted.

I found the interpretation of results on controls a bit confusing in the text. In 15 of the court-ordered sterilizations, 10 showed no visible change, while 5 showed slight enlargement due to 2 to 4 cystic follicles. Eleven patients with gynecologic problems showed no ovarian enlargement after a course of FSH. Ten patients were treated, 8 showed no enlargement, 1 slight change, and 1 marked enlargement. Is the effect, then, the degree of enlargement? Was the last patient who showed marked enlargement one who had undiagnosed bilateral polycystic ovaries? How could they determine it?

For determination of LH, the authors injected the extracts of 24 hour urine of patients with diagnoses of the Stein-Leventhal syndrome into immature rats. A qualitative result was obtained; if pronounced hyperemia and hypertrophy of the theca interna and little stimulation of the granulosa were obtained, the extract was judged LH in character. If many cystic follicles and pronounced stimulation of the granulosa obtained, the effect was judged primarily to be due to FSH. We have stated in several publications that in the true polycystic ovaries the follicles are inactive and do not secrete estrin. The authors confirm this opinion, showing that the follicles are in a state of stasis.

The authors suggest the use of FSH as a new diagnostic test, and my own reaction is—why? It is my opinion that they have omitted the most important test available, one we have repeatedly described: namely, the x-ray visualization of the enlarged ovaries. It is my feeling that visual diagnostic techniques are more valuable than the administration of a stimulating hormone to the ovaries, especially when only *questionable* enlargement may be present. My experience has been that the therapeutic administration of hormones to patients with the Stein-Leventhal syndrome is a rather expensive waste and, in addition, it may tend to delay the good results of surgical treatment.

DR. KEETTEL.—I would like to thank Dr. Stein for his remarks. We have not had experience with gynecography as a diagnostic aid. The patients suspected from history and pelvic findings of having the polycystic ovary syndrome were not subjected to exploratory laparotomy. The patients' urines were first examined for the presence of LH. If this was consistently found, the patients were tested with FSH. If there was a dramatic ovarian response to this hormone, we then were reasonably sure the patient had the syndrome and therapeutic surgery was recommended. It is true that these patients were operated upon at varying times following the FSH therapy. This was done to observe the histological response and the rapidity of regression.

We have been impressed with the fact that so few of the patients have definite ovarian enlargement on pelvic examination. Only 2 of our patients had ovaries that were definitely enlarged, 8 were felt to be slightly enlarged. Whether gynecography would have been helpful or not is questionable.

Other authors have indicated that there are a few patients with enlarged polycystic ovaries without any clinical signs of the syndrome. It is possible that the one control patient who had the marked ovarian enlargement after FSH therapy fitted into this group.

The amenorrhea seems to be the final phase of the polycystic ovary syndrome and perhaps some of our treatment failures fall into this group. Perhaps by our methods of detection patients may be treated earlier in the course of the syndrome with better therapeutic results. It should be emphasized that this paper is experimental and a preliminary report of our results.

DR. BRADBURY (Closing).—In this study we claim to have demonstrated luteinizing hormone (LH) in the extracts of urine from patients with the Stein-Leventhal syndrome. It seems appropriate to explain briefly what we interpret as LH. In 1937 Levin and Tynedale observed follicular development, ovarian enlargement, vaginal canalization, and uterine growth in immature mice given urine extracts. They found the uterine weight response to be the most consistent and sensitive tissue response to gonadotrophic extracts. In 1943, Klinefelter, Albright, and Griswold popularized the uterine weight response as an assay for follicle stimulating hormone (FSH). This was based on the assumption that FSH stimulates the ovary to produce estrogen which in turn causes a rapid increase in



uterine weight. The invalidity of this premise or the lack of specificity of the test is obvious when one observes that many investigators have used uterine weight response as an assay method for chorionic gonadotrophin. In the laboratory animal chorionic gonadotrophin is considered to be primarily LH.

In our tests we note the condition of the uterus, but are primarily concerned with the gross and histological responses of the immature rat ovary. Urine extracts from post-menopausal or castrate women are generally conceded to contain FSH. They cause a marked enlargement of the rat ovary and the increase in weight is due to the fluid accumulated in the many large cystic follicles. Grossly these ovaries are pale and edematous. Histologically there are many follicles with well-developed granulosa and most of the ova are normal. The theca interna is rather inconspicuous like a sheath of fibrous connective tissue.

Urine extracts from Stein-Leventhal patients produce responses in rat ovaries more closely resembling those produced by chorionic gonadotrophin. At autopsy the ovaries are grossly hyperemic and there may be relatively little increase in weight. Histologically there may be only 3 or 4 follicles that are stimulated or cystic but the theca interna is hypertrophied and very vascular. Many follicles that have just reached the stage of antrum formation show signs of atresia and the degenerating ova frequently have undergone segmentation. The uterine response of these animals offers ample evidence that estrogen was produced. Some laboratories might interpret these assays as due to FSH but our interpretation of the ovarian responses is based on their similarity to those induced by chorionic gonadotrophin and is considered as due to luteinizing hormone.

## INGUINAL SWELLING DURING PREGNANCY\*

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**A**N OVOID, reducible swelling in the inguinal canal during pregnancy constitutes at times an enigmatic problem for diagnosis. Even though coughing may cause transmission of an impulse to the examining finger, the first and seemingly apparent diagnosis, incomplete inguinal hernia, may be incorrect. Should accurate diagnosis elude the unwary, and ill-timed surgical treatment be attempted, the unexpected hazard of serious hemorrhage may beset the procedure.

This report considers 8 patients, observed through 21 pregnancies, in whom an inguinal mass was observed during the period of gestation. Two of the patients had bilateral inguinal protrusions. The incidence of inguinal protrusions was 1 in 1,021 deliveries during the 10-year period considered.

In every patient the first diagnosis was inguinal hernia. This proved to be correct in only 2 patients. One patient was found to have a myoma of the inguinal canal portion of the round ligament. Clinical evidence, in 5 others, seemed to indicate engorgement of dilated veins of the inguinal canal and round ligament as the cause of the inguinal swelling.

The relative importance of inguinal swelling as a complication of pregnancy varies according to diagnosis and medical council. Making the correct diagnosis has practical import over and above the desirability of being scientifically accurate. Knowing when to stay ill-timed surgical treatment is an obstetric responsibility. The high danger of retro- and intraperitoneal hemorrhage caused by ruptured uteroovarian veins, and the likelihood of this occurrence in patients who have excessive engorgement of pelvic veins may be emphasized by the development of an inguinal mass during pregnancy. This knowledge is the responsibility of the obstetrician.

This report concerns the differential diagnosis of three expanding intra-inguinal canal lesions, observed during pregnancy, and manifested clinically as protrusions of the inguinal area. Omitted from consideration are extra-inguinal canal lesions usually reviewed in the standard obstetrical textbooks, such as lipoma, inguinal lymphadenitis, vulvar varix, saphenous varix, cold abscess, and the occasional new growth.

Analysis of records indicates that the history and physical findings in incomplete inguinal hernia, intra-inguinal canal myoma of the round ligament, and dilated veins of the inguinal canal have both related and unrelated features.

\*Presented at the Twenty-fourth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 4, 5, and 6, 1956.

### Common Diagnostic Features

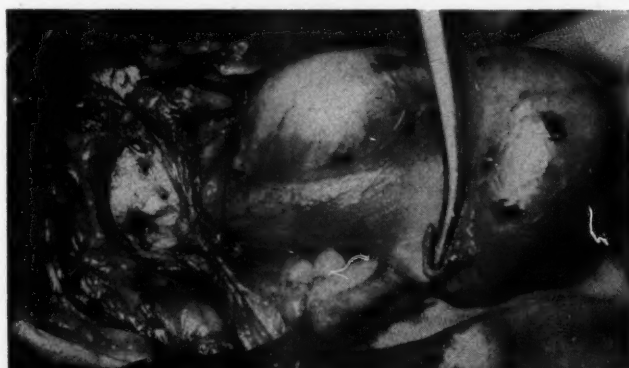
In all 8 patients the inguinal protrusion coincided in anatomical location with the inguinal canal; it was roughly ovoid in shape; and except for the patient with the myoma of the round ligament, it was reduced spontaneously, or by manipulation, with the patient recumbent.

On assumption of the erect position, pressure on the internal ring prevented its immediate return; coughing caused an impulse to be transmitted; and straining produced enlargement of the mass.

### Unrelated Diagnostic Features

Notwithstanding the striking similarity in physical findings, each diagnosis was supported by distinct variations in history and physical findings which were unique and of diagnostic significance.

A.



B.

Fig. 1.—A, Photograph of the myoma of the right round ligament showing its relationship to the inguinal ring. B, Bisected myoma of round ligament, right.

*A. Incomplete Inguinal Hernia.*—The 2 patients with incomplete inguinal hernia, observed through four pregnancies, were made aware of their affliction through the presence of an uncomfortable inguinal mass in the time prior to and between each intervening pregnancy. Each had been advised to submit to surgical repair. Failure of the hernia to become strangulated or cause pain led to postponement of treatment.

During pregnancy the protrusion of the hernia was present until some time between the twentieth and twenty-fourth weeks, when it suddenly disappeared. For the remainder of the period of gestation, no sign or symptom of inguinal hernia was demonstrable.

After delivery and soon following ambulation, the protrusion reappeared.

*B. Tumor of Round Ligament.*—One patient was observed to have an inguinal mass caused by an enlarging myoma of that portion of the round ligament contained within the inguinal canal. She first became aware of slight enlargement of the right inguinal area following operation for ruptured tubal pregnancy 3 years prior to the current pregnancy. Upon initial examination the mass was small and discrete. It enlarged slowly until the onset of the present pregnancy when the increment of growth became comparatively rapid.

The distinctive features of this inguinal protrusion were sharp outline of the border, solid consistency, and rubbery texture. On coughing a distinct impulse was transmitted. With recumbency the prominence of the mass diminished. This was because of recession of the mass into the inguinal canal.

When the gestation period reached 22 weeks, the myoma was excised. It was located within the inguinal canal with its upper pole attached to a small sac of peritoneum at the level of the internal ring (Fig. 1).

*C. Dilated Veins of the Inguinal Canal.*—Five patients demonstrated inguinal swelling which was presumed to be the result of dilated veins within the inguinal canal. In each patient the inguinal protrusion was anatomically distinct from enlargement resulting from varices of the vulva and varix of the saphenous vein in the fossa ovalis. In contradistinction to typical varices of the vulva, the inguinal protrusion, assumed to be caused by dilated veins of the inguinal canal, did not show dilated veins on inspection nor wormlike sensation to palpation.

Unlike patients with inguinal hernia and myoma of the round ligament, these 5 patients were entirely free of any protrusion of the inguinal area unless pregnant. The inguinal mass became apparent gradually and at first was not detected unless the patient was in the erect position. Enlargement was progressive until after delivery, when the mass suddenly and completely disappeared.

The onset of the inguinal protrusion varied according to time of gestation and parity. In primigravidas and "first time" multigravidas, its presence was generally first apparent after at least 28 weeks' gestation. In a multigravida who had developed an inguinal mass during a previous pregnancy, the onset of the inguinal protrusion occurred as early as 14 weeks' gestation, and its size was larger. Should a patient have previously developed an inguinal protrusion of this type, she was certain to have the same difficulty in a more pronounced form with each subsequent pregnancy. Once the pregnancy terminated, the inguinal protrusion consistently remained absent until the beginning of another pregnancy.

During pregnancy an inguinal protrusion assumed to be caused by dilated veins vanished upon recumbency and firm pressure on the internal ring prevented its immediate recurrence when the patient stood up. With the patient erect and the examining finger in the inguinal canal, coughing caused the transmission of an impulse which highly resembled that of an incomplete inguinal hernia. With less pressure from the examining finger at the internal ring, coughing sometimes caused a thrill-like impulse as the veins filled, a sensation previously described in conjunction with saphenous varix.<sup>1</sup> The typical gurgling characteristic of inguinal hernia was always absent.



### Comment

Several factors combine to confuse and make difficult the differential diagnosis of expanding lesions of the inguinal canal. It may be assumed that the disappearance of an incomplete inguinal hernia during midpregnancy results from torsion of the parietal peritoneum and the hindrance afforded by the enlarging uterus.<sup>2</sup> By the same measure, the explanations for the behavior of inguinal protrusions assumed to be due to excessive dilatation of the veins of the inguinal canal are considerably less well established and are quite controversial.<sup>3-8</sup>

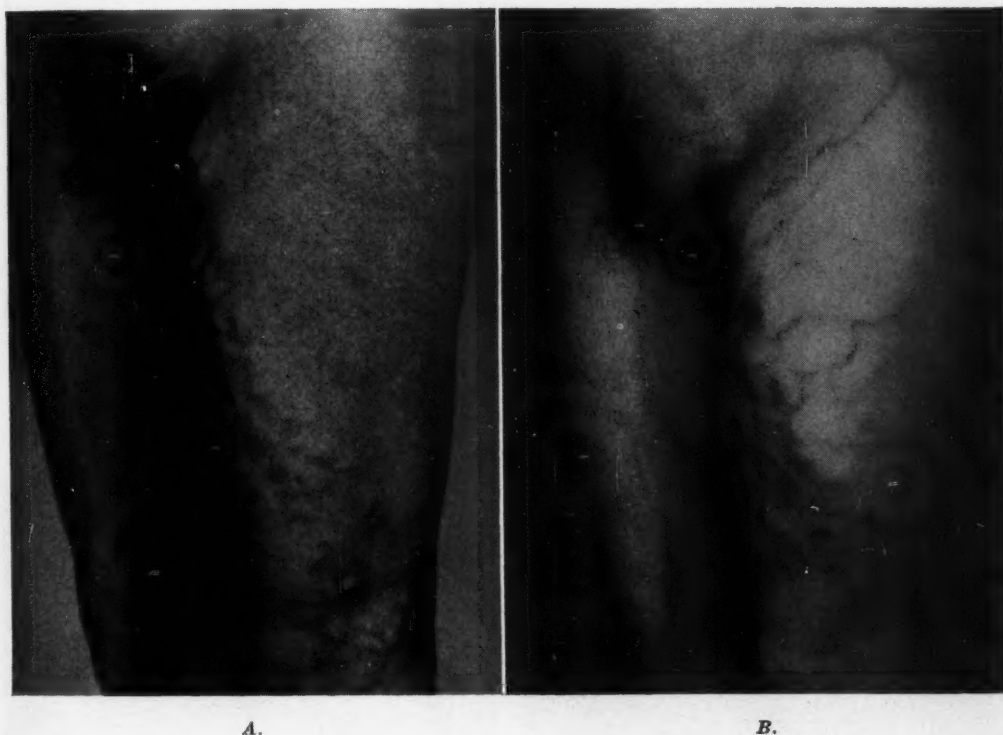


Fig. 2.—Dilated veins, left inguinal canal. A, Photograph using black and white technique.  
B, Photograph using infrared technique.

Efforts were made to demonstrate venous patterns in these three conditions by means of infrared photography.<sup>9</sup> Comparison of photographs taken with regular black and white film and those taken with infrared film demonstrates the added advantages of using the infrared technique for superficial venous patterns. Experience has shown the saphenous system to be highly photogenic with the infrared technique. Its value for contrasting the venous engorgement in inguinal canal lesions was limited and circumstantial. Although the veins of the inguinal canal were too deep to be demonstrated by means of infrared technique, some value was obtained from recording the degree of saphenous dilatation. Patients with inguinal canal vein syndrome demonstrated excessive saphenous varicosities which were frequently asym-

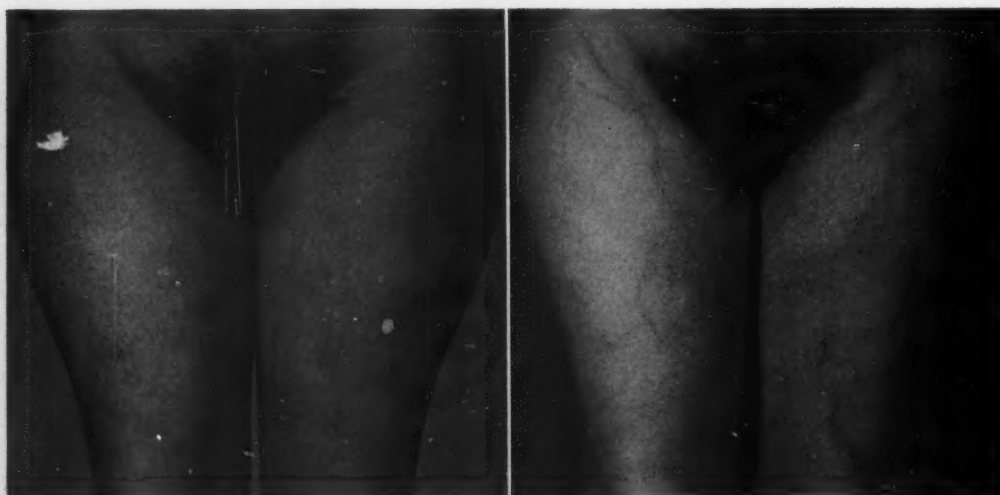
metrical and always maximal on the side of the inguinal protrusion (Fig. 2). When contrasted with photographs of a patient with a proved inguinal hernia (Fig. 3) and with those of the patient with the inguinal myoma (Fig. 4), the tendency toward excessive venous engorgement in the group showing inguinal swelling from dilated veins can be judged.



A.

B.

Fig. 3.—Inguinal hernia, right. A, Photograph using black and white technique. This picture was obtained one week after the hernia was reduced spontaneously. B, Photograph using infrared technique.



A.

B.

Fig. 4.—Myoma of round ligament, right. A, Photograph using black and white technique. B, Photograph using infrared technique.

It appears probable that the veins of the inguinal canal are in direct association with the uteroovarian system of veins rather than with the saphenous or systemic vein system. It was previously shown that evidence of functioning valves could not be demonstrated in the uteroovarian venous system.<sup>10</sup>

Pressure variations were directly and equally transmitted to the pelvic veins in both pregnancy and nonpregnancy. McLennan<sup>11</sup> showed the pressure in the saphenous system in pregnancy to be elevated three times above normal. This discrepancy was not found to exist in the uteroovarian system.<sup>12</sup> When the pressure in the uteroovarian veins was measured, the average during nonpregnancy was 14.62 cm. of water and during pregnancy 15.43 cm.<sup>12</sup> It was also shown that the volume capacity of the uteroovarian veins increased 66 times during pregnancy.

Immediately following evacuation of the uterus, the veins of the broad ligament collapse. The similar behavior, following delivery, of the inguinal protrusion caused by dilated veins supports the suggestion of an associated anatomical relationship between these two venous systems. Because of the absence of valves, it is probable that the impulse transmitted by coughing to the examining finger in the inguinal canal results from sudden increase in central pressure with direct peripheral dispersion. For this reason, the impulse in the dilated inguinal vein syndrome lacks the shocklike qualities noted in patients who have an inguinal hernia.

### Treatment

The treatment to be employed for relatively asymptomatic inguinal protrusions during pregnancy depends upon the etiology. The knowledge that incomplete, reducible inguinal hernias will probably become occult during the last half of pregnancy should temper the desire to repair this lesion surgically.<sup>16</sup>

Vignes<sup>13</sup> gave credit to Cruveilhier for first recognizing the inguinal vein syndrome and cited a case reported by Burchi of an inguinal swelling caused by dilated veins of the round ligament which was initially diagnosed as an epiploic hernia. Burchi attempted radical surgical treatment at which time the inguinal swelling was discovered to be caused by large varices of the round ligament. No hernial sac was identified. Recovery followed resection of the varices. Realization that the diagnosis may be erroneous because of possible confusion with the dilated vein syndrome makes the recommendation of surgical repair doubtful.

The prudent therapeutic program to be advised during pregnancy is watchful conservatism. Except for removal of tumors, operation for inguinal protrusions during pregnancy had best be avoided.

Prior to pregnancy, when possible, and always subsequent to delivery, strong recommendation should be given for repair of all hernias. Several cases of incarceration of the pregnant uterus in the sac of the hernia have been reported.<sup>14</sup> Robinson<sup>15</sup> reported upon a patient who was operated upon on the fifth postpartum day for a tender inguinal mass which proved to be caused by an incarcerated parovarian cyst and Fallopian tube.

Treatment for dilated veins of the inguinal canal during pregnancy is seldom necessary. Care must be practiced during delivery to reduce the possibility of rupture of the large veins. One of the 5 patients of the group observed in the present study developed a large retroperitoneal hematoma posterior to the right broad ligament. The hemorrhage developed incidentally

to a normal spontaneous delivery. She recovered slowly with complete resolution of the mass after a two-month period of guarded physical activity. Forceps delivery and extensive intravaginal manipulation should be avoided when possible because of the proclivity of the fragile veins to rupture.

### Conclusions

1. Three expanding lesions of the inguinal canal observed during pregnancy have been compared: incomplete inguinal hernia, fibromyoma of the round ligament, and dilated veins of the inguinal canal and round ligament.

2. All three caused an inguinal swelling simulating an incomplete inguinal hernia.

3. The significant disparate observations were: (a) incomplete inguinal hernia may suddenly disappear about midpregnancy to reappear after delivery; (b) an inguinal swelling caused from dilated veins is present only during pregnancy and generally appears about midpregnancy; and (c) tumors of the round ligament are never completely reduced, and the precise outline of the border can usually be distinguished.

4. Treatment, except for tumors, should follow a course of watchful conservatism.

### References

1. Watson, L. F.: *Hernia*, ed. 2, St. Louis, 1938, The C. V. Mosby Company, p. 39.
2. Watson, L. F.: *Hernia*, ed. 2, St. Louis, 1938, The C. V. Mosby Company, p. 163.
3. Baird, D., ed.: *Combined Textbook of Obstetrics and Gynecology for Students and Practitioners*, ed. 5, Edinburgh, 1950, E. & S. Livingstone.
4. Berkeley, C., Bonney, V., and MacLeod, D. D.: *The Abnormal in Obstetrics*, London, 1938, Edward Arnold & Co.
5. Gaudier: *Rev. chir.*, Paris 14: 859, 1894.
6. Verovitz, C. H.: *Diseases of Veins and Lymphatics of Lower Extremity*, Boston, 1941, The Christopher Publishing House.
7. Manley, T. H.: *M. News* 76: 130, 1900.
8. Tomkinson, J. S., and Winterton, W. R.: *Brit. M. J.* 1: 889, 1955.
9. Bowes, K., Riterband, S. H., and Andrews, J. E.: *J. Obst. & Gynaec. Brit. Emp.* 55: 285, 1948.
10. Hodgkinson, C. P.: *AM. J. OBST. & GYNEC.* 61: 321, 1951.
11. McLennan, C. E.: *AM. J. OBST. & GYNEC.* 45: 568, 1943.
12. Hodgkinson, C. P.: *Obst. & Gynec.* 1: 26, 1953.
13. Vignes, H.: *Arch. mal. coeur* 32: 478, 1939.
14. Boys, C. E.: *AM. J. OBST. & GYNEC.* 50: 450, 1945.
15. Robinson, S. C.: *Canad. M. A. J.* 68: 592, 1953.
16. Kuhn: *Gaz. méd. de Par.* 3 ser. 14: 797, 1859.

### Discussion

DR. C. D. DAVIS, Columbia, Mo.—Dr. Hodgkinson has been actively interested in venous pressures in ovarian veins for the past several years. Many have wondered from time to time concerning the practicality of this type of research, and not a few have considered it to be esoteric. However, when one stops to reflect on the occasional retroperitoneal hematoma that occurs the importance at once comes to the fore.

As far as I know, Dr. Lock of Bowman Gray School of Medicine was the first to report a maternal death which was due to rupture of the ovarian venous plexus. Last year, at one of the Maternal Mortality Committee meetings of the St. Louis Gynecological Society a case was presented that was very similar. Unilateral massive retroperitoneal hemorrhage, without rupture of the uterus, was the report at postmortem. It was not decided certainly whether it was rupture of the uterine or the ovarian veins but it surely seemed



to me to be part of the same situation that Dr. Hodgkinson is talking about. In this current article he briefly reports upon one patient who survived such an accident. I wonder if he feels that this occurs much more often than we have formerly supposed.

If the difference in venous return of the right and the left ovarian veins is as important in the etiology of varicocele and pelvic venous engorgement as we have been led to believe, then more of these swellings of the venous type would be on the left. Has that been your experience, Dr. Hodgkinson?

There seems to be little doubt about the conservatism recommended in inguinal hernia complicating pregnancy. Few of us have seen fibromyomas of the round ligament. I think, however, if we really pause to re-evaluate an occasional situation which heretofore had us puzzled, we might find it would fit into the pigeonhole that Dr. Hodgkinson has so aptly described. The one point I wish to re-emphasize is that once we suspect ovarian venous engorgement the threat of rupture during labor should be constantly kept in mind. In this way early recognition and definitive therapy may prevent fatal hemorrhage.

DR. HODGKINSON (Closing).—As to the frequency of ruptured uteroovarian veins in labor, it is difficult for me to give the precise figure. I believe they do occur perhaps more commonly than is recognized. At one time we reviewed 76 cases which had been reported in the literature. We observed 3 patients who had ruptured uteroovarian veins, one of which caused a fatality.

The question as to which is more common, the inguinal swelling on the right or left, as a result of these veins, is difficult for me to answer. Two of the patients observed in this present series had bilateral inguinal swelling, and I have observed it on the right when it was not present on the left.

We found that there was no difference in venous pressure between the right or the left ovarian veins.

I know that hemorrhage is not common, but it is a very important complication of labor, and certainly is something to be kept in mind if a patient suddenly goes into shock.

## CARCINOMA OF THE CERVICAL STUMP\*

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IN 1895 Alterthum<sup>1</sup> and in 1896 Chrobak<sup>2</sup> were apparently the first to publish a discussion of malignant lesions that developed in the cervical stump. From that time forward a number of publications have appeared on numerous problems connected with this particular condition. The incidence of the development of malignant lesions of the retained cervix brought on prolonged discussion regarding the merits of total versus subtotal hysterectomy. It is immediately apparent that it is extremely difficult to determine the exact incidence of the appearance of malignant lesions in the cervical stump, because there must be such a long period of observation of the patient. Figures quoted in the literature vary from 0.28 per cent of Fährndrich<sup>3</sup> to 2.0 per cent of Lahey.<sup>4</sup> The majority of analyses place the figure somewhere in the vicinity of 1.0 per cent.<sup>5-7</sup> This figure is not too remote from the usual quoted incidence in the population at large. At the present time there is little deviation from the dictum that total hysterectomy is preferable to subtotal hysterectomy except in very unusual circumstances. We can add little direct information to this because in the present series only 4.1 per cent (4 of 98 patients) had their subtotal hysterectomy performed at the Mayo Clinic. The remainder were referred for treatment of the malignant lesion at varying intervals after the subtotal hysterectomy had been performed elsewhere.

The other two major fields of discussion related to malignant lesions of the cervical stump have been the mode of therapy utilized and the prognosis. In much of the literature there has been considerable pessimism as far as both are concerned. The multiplicity of complications following radiation therapy to the cervical stump and the difficulties of surgical procedures in the pelvic area following a previous subtotal operation are well known and the generally poor survival rates have been felt to be directly related to them. The mode of therapy and the results of therapy will be the chief topics of this presentation.

From Jan. 1, 1940, through Dec. 31, 1949, a total of 1,451 cases of carcinoma of the cervix were seen at the Mayo Clinic. Of these, 98 were cases of carcinoma of the cervical stump, an incidence of 6.7 per cent. This is almost identical with the incidence of 6.4 per cent found in the series from 1915

\*Presented at the Twenty-fourth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 4, 5, and 6, 1956.

†The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

through 1930. Of these 98 cases, 84 fall into the category of "true" cases and 14 into the category of "coincident" cases of carcinoma of the cervical stump. For the analysis of this series, "coincident" cases were considered to be all cases in which the diagnosis of malignancy was made within 2 years from the time of operation. If the malignant lesion became apparent after this interval the clinically malignant lesion was presumed to have developed after the operation. It is difficult to compare different series of cases of carcinoma of the cervical stump from different institutions because the interval chosen varies with the author, but a 2 year interval seems to have become more widely used in recent publications. The main reason that a 2 year interval was chosen for this review was to aid in the comparison of our previously reported series from the Mayo Clinic in 1940.<sup>8</sup> In the present series only 14.3 per cent are "coincident" cases, while in the previous series 47.2 per cent fell into this category. This speaks well for the progress of the care and thoroughness of the gynecologic examination in the past 20 years. However, there is still room for improvement, for there is no excuse for cutting across an unsuspected carcinoma of the cervix during subtotal hysterectomy.

Table I shows the classification of the present series according to the type of malignant lesion present in the cervical stump, and the distribution between "true" and "coincident" cases. The two unknown cases were both far advanced and received only palliative roentgen therapy. It should also be stated that both of these occurred early in the decade and that with these two exceptions histologic proof of malignancy was present prior to the initiation of therapy.

TABLE I. CLASSIFICATION OF CARCINOMA OF THE CERVICAL STUMP TREATED AT THE MAYO CLINIC FROM JAN. 1, 1940, THROUGH DEC. 31, 1949

TYPE OF MALIGNANT LESION	"TRUE" CASES		"COINCIDENT"* CASES	
	NUMBER	PER CENT OF TOTAL CASES	NUMBER	PER CENT OF TOTAL CASES
Squamous-cell epithelioma	69	70.4	12	12.2
Adenocarcinoma	14	14.3	1	
Unknown	1		1	
Total	84	85.7	14	14.3

\*These cases were diagnosed as carcinoma within 2 years from the time of operation.

### Age Distribution

Table II shows the age distribution of the 98 patients under discussion at the time of diagnosis of carcinoma of the cervical stump. There was a slight difference between the average age of the patients with carcinoma of the cervical stump (53.0 years) and those in the series in general (49.0 years), but this is not felt to be significant. The majority of cases in both series fell between 40 and 60 years of age. The youngest patient was 35 years of age, and the oldest 77 years of age.

TABLE II. AGE INCIDENCE AT TIME OF DIAGNOSIS OF CARCINOMA OF THE CERVICAL STUMP

AGE (YEARS)	NO. OF CASES	PER CENT
30-39	6	6.1
40-49	28	28.6
50-59	37	37.8
60-69	24	24.5
70-79	3	3.0
Total	98	100.0

### Symptomatology

The symptoms which brought the patient to the physician are listed in Table III. These follow the pattern of symptoms of any cervical carcinoma. Vaginal bleeding is by far the most common complaint, with leukorrhea the second most common. It is of particular interest to note that 6 patients had no symptoms and routine examination resulted in the diagnosis of the cervical malignant lesion. The duration of symptoms varied over a wide span but the mean duration was relatively short. In this series, most of the patients seemed well aware that vaginal bleeding after subtotal hysterectomy is evidence of trouble.

TABLE III. SYMPTOMS AND DURATION OF SYMPTOMS PRIOR TO DIAGNOSIS OF CARCINOMA OF CERVICAL STUMP

SYMPTOM	NO. OF PATIENTS	DURATION OF SYMPTOMS	
		RANGE	MEAN (MONTHS)
Vaginal bleeding	75	3 days to 8 years	4
Leukorrhea	10	2 months to 10 years	3
Pain	6	1 month to 1 year	3
Patient felt tumor	1	1 day	
No symptoms (routine examination)	6		
Total	98		

### Parity

A surprising number of these women had never been pregnant or had had only one pregnancy, as shown in Table IV. It was thought that this might be explained by subtotal hysterectomy having been performed early in reproductive life. Therefore, the 21 nulligravid patients were investigated as to the age at the time of the subtotal hysterectomy, as shown in Table V. It is apparent from the table that this is not a valid explanation for the relatively low fertility in this group, since the average age at the time of operation was 44.0 years.

TABLE IV. DISTRIBUTION, BY NUMBER OF PREGNANCIES, OF PATIENTS WITH CARCINOMA OF THE CERVICAL STUMP

NO. OF PREGNANCIES	NO. OF PATIENTS
0	21
1	21
2	16
3	14
4	12
5	4
6	5
7	1
8	3
9	0
10	1
Total	98

TABLE V. NULLIGRAVID PATIENTS WITH CARCINOMA OF CERVICAL STUMP: AGE AT SUBTOTAL HYSTERECTOMY

AGE (YEARS)	NO. OF PATIENTS
30-39	4
40-49	14
50-59	3
Total	21



The reasons for the subtotal hysterectomy are listed in Table VI. The main reason given for the operation was the presence of fibromyomas, and certainly at the present writing this alone is not considered a valid reason for subtotal hysterectomy. The other major reasons were uncontrollable uterine bleeding and pelvic inflammatory disease. With increasing ingenuity in the use of hormones the former becomes more rarely necessary, and the antibiotics have, to a large extent, done away with the latter. It may be that in future series endometriosis may become the major indication for subtotal hysterectomy.

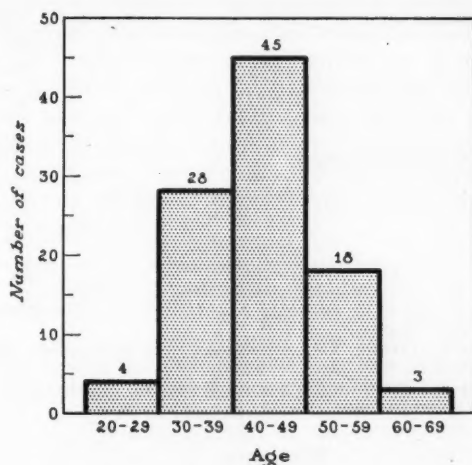


Fig. 1.—Age at time of subtotal hysterectomy.

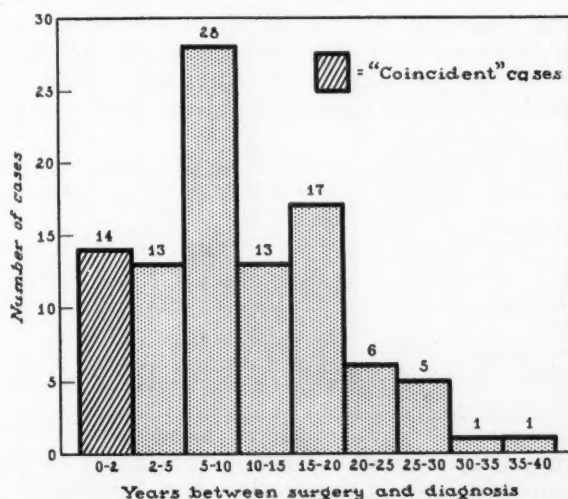


Fig. 2.—Interval between subtotal hysterectomy and diagnosis of carcinoma of the cervical stump.

It is depressing that 18 of 98 patients had no idea why the subtotal hysterectomy was done. It appears that this leaves a good deal of room for improvement in physician-patient communication.

The age of the entire group at the time of subtotal hysterectomy is shown in Fig. 1. The peak of the curve falls in the fifth decade, as might be expected. The average age for the group was 42.7 years.

Of particular interest is the interval which elapsed between the time of subtotal hysterectomy and the recognition of the cancer. This is shown in Fig. 2. The majority in this series were found 5 to 10 years after hysterectomy. There was an appreciable group whose clinical cancer appeared 15 to 20 years later and in one instance 35 years after hysterectomy. The average lapse of time after subtotal hysterectomy was 11.5 years.

TABLE VI. CARCINOMA OF CERVICAL STUMP: REASON FOR SUBTOTAL HYSTERECTOMY

REASON FOR HYSTERECTOMY	NO. OF PATIENTS
Fibromyomas	46
Uterine bleeding	13
Pelvic inflammation	14
Prolapsus uteri	2
Endometriosis	1
Pregnancy (Porro cesarean hysterectomy)	1
Carcinoma of cervix*	1
Adenocarcinoma of fundus†	1
Uterine malignancy (?)‡	1
Unknown	18
Total	98

\*Radium therapy 3 years prior to subtotal hysterectomy. Recurrence (?) of squamous-cell epithelioma 20 year later.

†Squamous-cell carcinoma, Grade IV, of cervix 3 years after subtotal hysterectomy. Original slides of fundus obtained and they showed adenocarcinoma, Grade I.

‡Seven years after subtotal hysterectomy squamous-cell epithelioma of cervix developed. Original malignant lesion, type unknown.

### Therapy

The treatment utilized at the clinic for carcinoma of the cervical stump has been radiation therapy for the majority of patients, as shown in Table VII. In only 5 of 98 cases was any form of surgical procedure performed. This consisted of abdominal removal of the cervical stump and in three instances radical removal of the pelvic lymph nodes as well. Eighty-one of the 98 patients were treated by means of combined radium and roentgen therapy.

TABLE VII. THERAPY OF CARCINOMA OF THE CERVICAL STUMP

THERAPY	"TRUE" CASES	"COINCIDENT" CASES
Radium therapy alone	7	2
Roentgen therapy alone	3	
Radium and roentgen therapy	71	10
Surgical treatment alone	2	1
Surgical treatment and roentgen therapy		1
Surgical treatment, radium and roentgen therapy	1	
Total	84	14

The usual technique of radiation therapy for cancer of the cervix at the Mayo Clinic has been described in detail elsewhere by two of us.<sup>9</sup> Briefly it consists of an intensive divided-dose application of radium with coincident roentgen therapy. In the treatment of cancer of the cervical stump certain modifications must be made in this scheme.

In the first place additional care must be used in packing off the radium applicators from the bladder and rectum. This is particularly important, since with the removal of the fundus of the uterus the radium source may be closer to loops of bowel, and also with the scarring subsequent to pelvic operations the normal anatomic relationships are more likely to be distorted. The unit of radium treatment is the 50 mg. tube filtered with 1 mm. of platinum.

Radium treatments are given two to three times weekly. Total dosage is usually in the vicinity of 4,000 mg. hr. and treatment lasts 2 weeks. This varies somewhat, depending on the bulk and location of the lesion. The roentgen therapy is administered to two anterior and two posterior pelvic ports. At present, daily treatments of 200 r (air) are delivered at 50 to 70 cm. distance to each of two ports for a total dose of 2,000 to 2,400 r per port, employing 250 kv. (peak) radiation with half-value layer of 1.3 mm. of copper. The technique, nearly to the end of this study, consisted of four daily treatments at 200 kv., 50 or 70 cm. distance, half-value layer of 1.0 mm. of copper, 540 r (air) to each of four pelvic fields following radium treatment. After the course of treatment patients are examined every 3 months during the first year, with careful pelvic examination, visualization of the cervix and biopsy if indicated. If the course is satisfactory during this interval the patients are seen twice during the next year and yearly thereafter. As has been stated, this method relies more on the radium therapy than many other techniques. The roentgen therapy is utilized chiefly in an attempt to control the spread of cancer to the pelvic nodes.

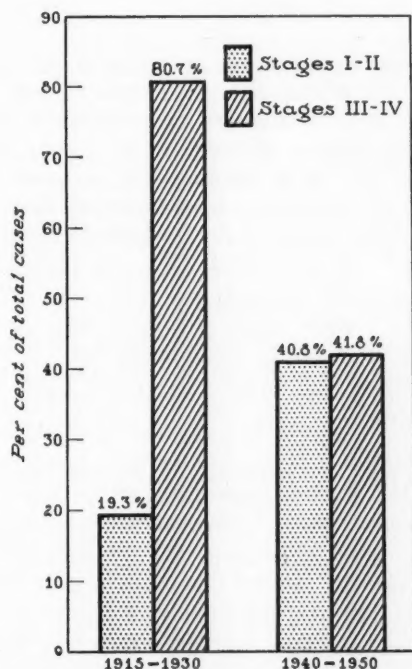


Fig. 3.—Comparison of carcinoma of the cervical stump by stage of lesion in 1915-1930 and 1940-1950.

### Results of Treatment

The late results of treatment in the "true" cases are shown in Table VIII. Thirty-five of the cases of squamous-cell carcinoma fell in the relatively favorable Stages I and II and 34 in the more advanced Stages III and IV. It is particularly difficult to stage these lesions accurately, because so often the pelvis is markedly altered by the previously present disease and by the surgical treatment attempted for that condition. These lesions were independently staged by a gynecologist and a radiologist, and the staging shown in these tables is a combination of these two independent evaluations. Of 84 patients,

76 (90.5 per cent) were considered to be successfully followed. Fifty-one of these survived for 5 years or more with an over-all survival rate of 67.1 per cent of the traced patients. If all patients not traced are considered dead of the carcinoma, the absolute survival rate is 60.7 per cent.

TABLE VIII. FIVE-YEAR RESULTS OF THERAPY: CARCINOMA OF THE CERVICAL STUMP: "TRUE" CASES

TYPE OF MALIGNANT LESION	TOTAL PATIENTS	TRACED PATIENTS	PATIENTS SURVIVING FOR 5 YEARS	
			NUMBER	PER CENT OF TRACED PATIENTS
Squamous-cell epithelioma,				
Stage I	8	7	7	100.0
Stage II	27	23	21	91.3
Stage III	19	18	12	66.7
Stage IV	15	13	4	30.8
Adenocarcinoma	14	14	7	50.0
Unknown	1	1	0	0.0
Total	84	76	51	67.1

This represents a highly satisfactory increase in salvage over the 26.3 per cent 5 year survival rate noted in the group previously reported from 1915 through 1930. It appears that there are two major reasons for this: First, as shown in Fig. 3, a much higher percentage was seen relatively early in the course of the disease, 40.8 per cent versus 19.3 per cent in the earlier series. Second, we believe that this represents an increased skill in the utilization of radium and the recognition of satisfactory radiation response in the tumors.

In the 14 "coincident" cases (Table IX), all patients were satisfactorily traced for 5 years or more and the survival rate was 42.9 per cent. This is significantly lower than the "true" case survival rate, as might be expected.

If the entire group of 98 cases is considered, 90 (91.8 per cent) were successfully traced, with a relative survival rate of 63.3 per cent and an absolute survival rate of 58.2 per cent.

TABLE IX. FIVE-YEAR RESULTS OF THERAPY: CARCINOMA OF THE CERVICAL STUMP: "COINCIDENT" CASES

TYPE OF MALIGNANT LESION	TOTAL PATIENTS	TRACED PATIENTS	PATIENTS SURVIVING FOR 5 YEARS	
			NUMBER	PER CENT OF TRACED PATIENTS
Squamous-cell epithelioma,				
Stage I	2	2	2	
Stage II	3	3	1	
Stage III	3	3	2	
Stage IV	4	4	0	
Adenocarcinoma	1	1	1	
Unknown	1	1	0	
Total	14	14	6	42.9

### Conclusions

It is to be hoped that we are reporting on a vanishing condition and that in the years to come only scattered case reports of carcinoma of the cervical stump may appear. With rare exceptions, all of these patients would have



been cured by the simple expedient of total hysterectomy at the time of the original operation. With the wider use of the cervical smear for cytology and the recognition of preclinical carcinoma of the cervix this situation will become more unusual. Carcinoma of the cervical stump remains a problem necessitating the highest diagnostic skill of the gynecologist and the most competent therapeutics of the radiologist. The complications incident to treatment will be discouragingly high if this combination is not observed. However, with careful and accurate treatment satisfactory survival rates are possible.

### Summary

Ninety-eight cases of carcinoma of the cervical stump, seen at the Mayo Clinic from Jan. 1, 1940, through Dec. 31, 1949, have been reviewed. Of these, 84 were "true" cases and 14 were "coincident" cases. The relative survival rate for the entire group was 63.3 per cent and the absolute survival rate 58.2 per cent.

### References

1. Alterthum: Quoted by Stark, Georg: *Zentralbl. Gynäk.* 61: 1528, 1937.
2. Chrobak, R.: *Monatschr. Geburtsh. u. Gynäk.* 3: 177, 1896.
3. Fährdrich, Joachim: *Ztschr. Geburtsh. u. Gynäk.* 109: 382, 1934.
4. Lahey, F.: Quoted by Behney, C. A.: *AM. J. OBST. & GYNEC.* 40: 780, 1940 (closing discussion).
5. Witte, D. H., and Ovitt, D. W.: *J. Internat. Coll. Surgeons* 15: 313, 1951.
6. Pearse, R. L.: *Surg., Gynec. & Obst.* 58: 845, 1934.
7. Von Graff, Erwin: *AM. J. OBST. & GYNEC.* 28: 18, 1934.
8. Fricke, R. E., and Bowing, H. H.: *Am. J. Roentgenol.* 43: 544, 1940.
9. Fricke, R. E., and Decker, D. G.: *Am. J. Roentgenol.* 75: 502, 1956.

### Discussion

DR. JOSEPH W. KELSO, Oklahoma City, Okla.—I envy the opportunity of the authors in their association with an institution of such volume of patients that they can report 98 cases of a given rare lesion coming under their care in 10 years. Such institutions have the privilege of offering answers to perplexing problems.

I feel impelled to question the validity of their end results when reported on traced cases only. If that method of obtaining results is accepted, we shall be compelled to change our entire basic concept of reporting survival rates.

A great many of you know that for the past 11 years I have been managing all cases of carcinoma of the cervix, in which I had reason to believe I could remove the existing lesion, by a radical hysterectomy, bilateral lymphadenectomy, and removal of a liberal portion of the vagina, followed by deep x-ray therapy. To date, I have operated upon 172 patients, and in this group there have been 11 with cervical-stump malignancy, all of which patients are alive.

If you will permit me to add a patient who lacks 5 weeks of having reached her 5 year mark, I should like to present for your comparison 5 patients who were operated upon by me 5 or more years ago who are alive and well. Three of these cases were classified as International Stage II. Both of those classified as International Stage I were far enough advanced to have been classified as Group II, Schmitz classification. If I am correct in my determination, Dr. Decker's Stage I International survival percentage would be 87.5 per cent and for Stage II International 77.7 per cent, which we must admit is enviable. I hope that my cases will keep pace with those figures as my group enlarges. However, Dr. Decker fails to classify for us the cases of adenocarcinoma. Had he done so, his figures would, I believe, lose some of their challenge. Likewise, it is rather difficult for me to believe that our clinical estimations completely agree when he has only 8 cases classified as

Group I International, when he relates that 6 of their patients had no symptoms and were picked up on routine examination, and when he states that 2 cases were apparently so early in their invasion that the attending staff thought they could be cured by a trachelectomy.

I have repeatedly contended that results should be compared with those obtained by other methods of treatment in the local community, since many patients cannot go to distant clinics for treatment, even if they might desire to do so. I have reviewed the cervical-stump malignancies treated on our gynecological service at the University of Oklahoma School of Medicine by other members of our staff, encompassing a period of time similar to that of my surgical patients, who have been managed 5 years or more. This group comprises 24 cases, 14 of which were true stump malignancies and 10 were "coincidental" cases. I regret to state that the results do not compare favorably with those of Dr. Decker. There are only 8 of these patients alive and well today, although 2 who died 4 years after treatment were free of demonstrable evidence of their disease at the time of death. With these 2 cases added to the survival group, the percentage of 33.3 per cent is brought up to 41.6 per cent of apparently cured cases. One of these patients died from cardiovascular disease, and the other bled to death from a duodenal ulcer. Two deaths occurred as a direct result of their treatment, these patients dying from intestinal perforation. Another died from ureteral obstruction, which was thought to have been the result of her therapy.

DR. RICHARD L. MEILING, Columbus, Ohio.—At the Gynecological Tumor Clinic of the Ohio State University College of Medicine we have treated 73 patients with carcinoma of the cervical stump in the years 1940 to 1956, inclusive. (Eight patients have been treated so far in 1956.) In this same period of time, namely, 1940 to July, 1956, we have treated a total of 816 patients for carcinoma of the cervix of all types and stages. This, then, presents us with an incidence of carcinoma of the cervical stump of 8.9 per cent of our cases. Our 5 year survival rate for patients with carcinoma of the cervical stump is 36.3 per cent. Allow me to present for comparison the 5 year survival rate in the University Gynecological Tumor Clinic at Ohio State University:

Stage 0	96.2%
Stage I	81.4%
Stage II	48.5%
Stage III	21.4%
Stage IV	2.5%

It is our firm belief that prevention is the best therapy available for these patients and we advocate total or panhysterectomy in all patients requiring hysterectomy. At the University Hospital during the period 1948 to 1955, inclusive, there were 1,253 panhysterectomies and 21 supracervical hysterectomies performed. (At this point I might further state that during 1955 no supracervical or subtotal hysterectomies were performed in University Hospital.)

These were patients with nonmalignant conditions of the cervical stump who, in our clinical evaluation, presented sufficient cervical disease to warrant surgical removal of the cervix. It is obvious that the vast majority of patients sent to us with cervical stump carcinoma or for cervicectomy were referred from other hospitals where subtotal hysterectomies are still being performed. In the period 1940 to 1956, inclusive, a total of 214 patients were operated on in Ohio State University Hospital for cervicectomy.

#### CARCINOMA OF THE CERVICAL STUMP, OHIO STATE UNIVERSITY HEALTH CENTER, 1940-1956

Treated cases (stump)	73
Five-year survival rate (12 out of 33 patients)	36.3%
Total cervical cancer treated	816
Per cent cancer of stump	8.9%

DR. HERBERT E. SCHMITZ, Chicago, Ill.—The authors have had the finest end results that I have seen. I also wish to say how very pleased I am with the fact that a clinic so well equipped, surgically, as the Mayo Clinic, has seen fit to continue to treat cervical stump cancer by means of irradiation. Many of you know that I have been a strong advocate of irradiation therapy, but we have also carried on a very extensive program of surgical treatment of cancer of the cervix. I do not feel that I am biased one way or the other.

The one thing that I do think we must get over is this pitting of one method of treatment against the other. It seems that whenever we arrange a program, we have those on the surgical side and we have those on the radiological side. I think that is a detriment. They have to be used together. There are certain cases where surgery is definitely indicated, but as a primary approach I believe that irradiation therapy has its place and will continue to occupy that original place of preference.

We know that surgical series have to be selected. Just this last week, at a meeting of the pelvic surgeons in New York City, Brunschwig reported on his work, Meigs reported on his, Gene Bricker on his, and then Kottmeier brought the statistics from the Radiumhemmet, and there just is not any comparison. With the Radiumhemmet statistics, every patient is accounted for. The surgical group, admittedly, is a selected group, and the selectivity is either in the outpatient clinic or in the patients who are admitted on the service, or the patients admitted for irradiation or for surgical therapy, rather. So there is not any comparison.

Dr. Kelso is a very excellent surgeon, and in his over-all report of his surgical endeavors he has brought forth some very fine salvage rates, but when you can have over 50 per cent salvage with irradiation therapy, in all of the patients who are admitted into the clinic, then we have really attained something worth while.

DR. C. GORDON JOHNSON, New Orleans, La.—I wish to give to you a philosophy at Tulane regarding hysterectomy, particularly with reference to its use as a prophylaxis for a carcinoma of the cervical stump.

For many years we were not particularly satisfied with the results of hysterectomy, particularly as far as the mortality rate of the subtotal operation was concerned. We felt we could reduce the mortality from subtotal hysterectomy, possibly by doing away with the operation completely. This we have done, beginning in January, 1952. We tried to make it 100 per cent 2 years prior to that time, beginning actually in 1950, but there was one subtotal hysterectomy done in both 1950 and 1951. This is on the Tulane service at Charity Hospital.

I wish to show you the slides for the last 15 years, showing the decline in subtotal hysterectomies up to the present point, where, in the last 5 years (which will be concluded in December of this year) there have been no subtotal hysterectomies done.

This edict was set down by the chairman of our department, and it was agreed upon by all members of the staff. We realize that perhaps it may not be agreed upon by everyone here, but we felt it was the only way we could determine whether or not the mortality in total hysterectomy would be greater than or equal to that of subtotal, by doing all hysterectomies totally, not using the excuse that we had pelvic inflammatory disease with extensive adhesions, or that we had endometriosis that involved a rectovaginal septum, or that we had enlargement anywhere.

One hundred hysterectomies had been done on the Tulane service beginning January, 1952. You will notice on this slide that these are what you might say were prewar years. Approximately 40 per cent of the hysterectomies were abdominal, and I might add that this is a treatment of benign disease. I have not included hysterectomies for malignant disease in these slides.

During the war years, the subtotals are approximately one-half of what they were in the 2 years prior. Notice that the mortality for the subtotal hysterectomies in this period was

zero, whereas in the one prior to that it was over 1 per cent. The mortality for all abdominal hysterectomies was less than 1 per cent.

In the next period, there were 1,246 hysterectomies, which included 436 vaginal operations, with roughly 900 abdominal hysterectomies, 100 per cent total, with a mortality of 0.6 per cent.

Since this slide, which now extends an additional 2 years, there has not been a sub-total hysterectomy done on the Tulane service, and the mortality still remains around 0.5 per cent.

As far as the treatment of stump carcinoma is concerned, we feel that in the majority of instances it is better handled by radiation, followed by excision of the stump and pelvic lymph gland dissection.

DR. HUNT (Closing).—After all, I suppose in appraising results of therapy in carcinoma of the cervix, the single most important statistic is the 5 year survival rate for all groups, because that does away with the confusion of the staging, and it is a figure on which one can hang his hat, so to speak.

I feel that Dr. Schmitz has reiterated the necessary admonishment that surgery and radiation therapy should be cooperative things.

Dr. Kelso's 100 per cent 5 year survival on a small series of cases could hardly be improved upon, and it is excellent. It must be mentioned that these are selected cases in Stages I and II.

He did comment that Dr. Decker talked about traced patient survival in the paper—that is, relative survival—and that is true. He reported it that way, but he also reported the absolute survival by calling all untraced patients dead. That figure for all the group, again, was 58.2 per cent.

Dr. Meiling reported a rather high incidence of this type of carcinoma of the cervix, which he felt was nearly 3 per cent more than ours.



## DYSFUNCTIONAL UTERINE BLEEDING IN THE PREMENOPAUSAL AND MENOPAUSAL YEARS\*

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THE term "functional uterine bleeding" is applied to those cases of abnormal bleeding for which no other diagnosis can be found. The cause is still poorly understood. The number of patients embraced by this "catch-all" diagnosis is being reduced. With the ever-advancing knowledge in endocrinology and pathology, the true nature of the disease process causing the abnormal bleeding is becoming increasingly obvious. Moreover, further studies, such as biopsy, Papanicolaou smears, curettage, culdoscopy, and exploratory laparotomy, frequently disclose the true nature of the illness.

We will review 222 cases of "functional uterine bleeding" in the premenopausal and menopausal years, and compare the findings with those of a similar series in a younger age group. Since the average age of menopause in the American white woman is 46, it appears that age 40 would be the beginning of the premenopause. This figure, however, is arbitrary.

### Materials and Methods

We have 222 women of age 40 and older, excluding postmenopausal patients, admitted to the Methodist Hospital, Houston, Texas, from 1952 to 1954. Recurrence of bleeding a year or more following the last episode is considered to be postmenopausal, and is not included in this study.

The diagnosis on admission in all of these patients was "functional uterine bleeding—cause undetermined." They were white with a few Latin Americans, and the overwhelming majority were private patients under the care of their own private physicians, since the Methodist Hospital has an open staff with a small clinical service. Each of these women had an essentially normal pelvic examination recorded at the time of admission.

The total number of gynecological admissions during this time at Methodist Hospital was 3,180. Hence, the incidence of functional uterine bleeding in the premenopausal and menopausal years in this series was 6.9 per cent of all gynecological admissions.

*Age Spread and Parity.*—The youngest patient in this group was 40 years old and the oldest 56. One hundred and three were 40 to 47 years old, 88 were 47 to 50 years old, and 31 were 50 years of age or older. There were 43 patients who were nulliparous and 122 were parous. The parity ranged from 1 to 6, but the parity of 57 patients was not known. No significance could be attached to fertility.

\*Presented at the Twenty-fourth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 4, 5, and 6, 1956.

*Method of Therapy.*—Table I shows the therapy administered and refers to the primary treatment on one visit to the operating room. Several patients were brought back for procedures at a later date.

TABLE I. OPERATIONS PERFORMED

Curettage and cervical biopsies	106
Curettage only	76
Preliminary curettage, followed by:	
a. Vaginal hysterectomy with repair	8
b. Abdominal hysterectomy with adnexectomy	9
c. Abdominal hysterectomy without adnexectomy	8
d. Anterior and posterior vaginal repair	8
Primary vaginal hysterectomy with and without repair	3
Primary abdominal hysterectomy with adnexectomy	3
Primary subtotal hysterectomy without adnexectomy	1
Total cases	222

*Endometrial Picture.*—Table II demonstrates the endometrial picture. When compared with a similar study of functional uterine bleeding in younger women,<sup>1</sup> it becomes clear that the incidence of endometrial hyperplasia is much higher in the older age group; for instance, 20.7 per cent as compared with 13.9 per cent. In the younger group there was no atypical hyperplasia, while in this group there were 17 cases, including 6 associated with frank adenocarcinoma in the same uterus.

TABLE II. MICROSCOPICAL FINDINGS

	NO. CASES	% OF TOTAL
Proliferative endometrium	75	33.8
Secretory endometrium	56	25.8
Mixed secretory and proliferative	18	8.6
Endometrial hyperplasia (total)	50	20.7
Cystic hyperplasia	33	
Atypical hyperplasia	11	
Atypical hyperplasia with adenocarcinoma	6	
Atrophic endometrium	7	3.4
Decidual reaction	3	1.3
Insufficient for diagnosis	13	6.4

Table III shows the endometrial picture encountered in a similar study of functional uterine bleeding in women younger than 35.<sup>1</sup> It appears that unopposed estrogen stimulation of the endometrium is of more consequence in this age group than in the younger one. Of the 17 patients with atypical endometrial hyperplasia in the older group, only 6 were younger than 47, while 11 were above this age. Seven of these 11 patients were 50 or more years old.

TABLE III. ENDOMETRIAL PICTURE ENCOUNTERED IN PATIENTS WITH FUNCTIONAL UTERINE BLEEDING UNDER THE AGE OF 35 (JACOBS AND LINDLEY<sup>1</sup>)

	TYPE OF ENDOMETRIUM				
	PROLIFERATIVE	SECRETORY	MENSTRUAL	BENIGN CYSTIC HYPERPLASIA	MIXED
Percentage	49.0	21.5	3.9	13.93	9.8

Apparently this condition becomes more prevalent in patients with a late menopause, a factor which has already been stated to bear some relationship

to adenocarcinoma of the endometrium. A large number of the endometria were progestational; even more than in the younger group, e.g., 25.8 per cent as compared with 21 per cent. This may indicate that functional uterine bleeding in the presence of ovulation is fairly common and that ovulation may occur far into the menopausal years.

A recent study by McKay and associates<sup>3</sup> shows that the early stages of endometrial cancer bear a histochemical resemblance to progestational endometrium and indicates there is a possibility of a progesterone-like hormone in the genesis of endometrial cancer. Our assumption, therefore, that progestational endometrium means ovulation has occurred may not necessarily be true, but may rather indicate some source other than the corpus luteum from which this progesterone-like hormone may originate.

Many reports have cited the fact that women with a "bloody menopause" have a high incidence of endometrial cancer. The 25.8 per cent occurrence of progestational endometrium and the previously noted association of the bloody menopause and adenocarcinoma may prove to be a link in the genesis of endometrial cancer. This type of endometrial response, therefore, may ultimately be taken out of the functional uterine bleeding category.

### Unrecognized Organic Pathology

As previously stated, functional uterine bleeding is an elimination diagnosis. Even though all 222 patients were thought to have an essentially normal pelvic examination prior to admission, subsequent examination proved otherwise in a large percentage.

Table IV shows the type of change discovered at examination under anesthesia, curettage, and/or biopsy, and exploration of the pelvis. This list of organic pathology excludes pelvic relaxation and cervicitis, the latter being present to a degree in practically all. Organic pathology was demonstrated as a possible cause of abnormal bleeding in 30.2 per cent, while in the younger age group its incidence was only 17 per cent. Without doubt, as time progresses, more patients in the older age group will have a recurrence of their bleeding, and it will be discovered at some later date that organic disease is present. Our feeling is that atypical endometrial hyperplasia should be considered as an anatomical diagnosis and not as a functional disturbance.

TABLE IV. ASSOCIATED PATHOLOGICAL FINDINGS

PATHOLOGICAL FINDINGS	NO. CASES
<i>Benign.</i> —	
Multiple uterine myomas, all varieties	28
Adenomyosis	9
Endometriosis	2
Endometrial polyps	3
Endocervical polyps	2
Dermoid cyst	1
Brenner tumor	1
Pseudomucinous ovarian cyst	1
Atypical hyperplasia	11
<i>Malignant.</i> —	
Adenocarcinoma of endometrium	6
Invasive squamous-cell carcinoma of cervix	1
Carcinoma in situ of cervix	2
Total organic pathology	67 (30.2%)

There were 9 cases of previously unsuspected malignancy in this series, an incidence of 4.05 per cent. Six of these were adenocarcinoma of the endometrium, 2 were carcinoma in situ of the cervix, and one was invasive carcinoma of the cervix.

Of the 6 cases of adenocarcinoma of the endometrium, 2 were treated with intracavitary radium followed by complete pelvic surgery, and 3 by complete surgery alone. The one instance of invasive carcinoma of the cervix was discovered in the curettings of the endocervical canal rather than by biopsy of the external os. This patient was treated by radium.

The 2 cases of carcinoma in situ of the cervix were diagnosed by biopsy of the external os and were treated by hysterectomy after knife conization was done to rule out invasion. It is problematical whether or not the carcinoma in situ played any part in the patient's bleeding. Many women have been seen with a final diagnosis of carcinoma in situ who presented abnormal bleeding as their primary complaint. The endometrial picture in these 2 patients was proliferative and mixed endometrium, respectively. No other significant findings were demonstrated.

A point worthy of consideration is whether or not some agent other than the intraepithelial carcinoma may produce the abnormal bleeding. Many patients with carcinoma in situ will present abnormal bleeding as the main symptom and no other cause will be found. Whether or not the endometrium plays a part in such bleeding is questionable. This makes one wonder whether a carcinogenic agent may precipitate the abnormal bleeding.

#### Endometrial Hyperplasia

Of the 50 cases of endometrial hyperplasia, 33 showed benign cystic hyperplasia, 11 atypical hyperplasia alone, and 6 atypical hyperplasia in combination with adenocarcinoma of the endometrium. Our criteria for diagnosing atypical endometrial hyperplasia are the following: (1) abnormal numbers of glands with adenomatous hyperplasia, (2) cellular atypism in the glands, and (3) the presence of squamous plaques in a significant number of glands.

It is our impression that atypical hyperplasia should be considered as a premalignant lesion. Novak<sup>2</sup> has recently published a study of postmenopausal and endometrial hyperplasia. His findings indicate that the clinical features in these patients closely resemble those in patients with adenocarcinoma of the endometrium. He believes that the hyperplasia and adenocarcinoma result from varying degrees of response to the same stimulus. Adenocarcinoma, therefore, is merely an exaggerated response to that stimulus.

We are presently engaged in an investigation along the same lines as Novak's on endometrial hyperplasia in the premenopausal and menopausal years, the results of which will be the subject of a later report.

It is our belief that benign cystic hyperplasia is no cause for alarm unless the bleeding persists or recurs after curettage. Of the 12 cases of atypical hyperplasia without adenocarcinoma, 9 were treated by total hysterectomy after the diagnosis was made from curettage and biopsy. Three of these patients received no therapy other than curettage and biopsy.

#### Comment

We believe that the term "functional uterine bleeding" is not applicable to patients in the premenopausal and menopausal years, just as it is not tenable in reference to postmenopausal bleeding. Our findings suggest correlation of certain well-known clinical observations. First, a large percentage of such patients will be found to have organic pathology; and, second, abnormal bleeding (in all age groups) even in the absence of organic pathology, may



bear an ultimate relationship to endometrial cancer. Neoplasia of the endometrium is a classic example of a true polyglandular endocrinopathy. It is well known that cancer of the endometrium is more than coincidentally associated with endocrine stigmas such as diabetes, hypertension, obesity, low fertility ratio, chronic cystic mastitis, and endometrial hyperplasia. The recent study of McKay and associates indicates that endometrial cancer bears a histochemical relationship to progestational endometrium.<sup>3</sup> This observation, coupled with our findings that a high percentage of patients with a "bloody menopause" show progestational endometrium, perhaps indicates that such a progestational endometrium may not necessarily mean ovulation has occurred. It may rather call attention to the fact that a progesterone-like hormone is possibly involved in the production of a "bloody menopause" and may eventuate in endometrial cancer. This is hypothetical but suggests a possible link in the genesis of endometrial cancer.

#### Plan of Management

A patient with irregular premenopausal or menopausal uterine bleeding should be carefully screened prior to hospitalization. A careful history, to rule out exogenous steroids, and detailed pelvic examination, including, when indicated, cervical biopsy, Papanicolaou smears, and/or endometrial biopsy, are recommended. We would like to emphasize the importance of endometrial biopsy as a screening procedure in the office or outpatient clinic. This may be employed with or without suction with the use of the Randall or Novak type of endometrial biopsy curette. Clyman<sup>4</sup> has recently described an excellent endometrial biopsy instrument which offers a great many advantages. The Clerf cancer-cell specimen collector is a valuable addition to the use of suction.

This method of screening, if positive for endometrial carcinoma, means that the patient will be saved an anesthetic, and an additional operative procedure. A negative endometrial biopsy does not rule out endometrial cancer and makes diagnostic curettage mandatory. Following such negative screening procedures, the patient should have a fractional diagnostic curettage with multiple biopsies of the cervix and careful examination under anesthesia. If organic pathology is discovered as the cause of the bleeding, appropriate treatment should be instituted.

We wish to submit that atypical hyperplasia in this older age group should be considered as premalignant and warrants treatment by total hysterectomy, either vaginal or abdominal, depending on the preference of the operator.

If a benign endometrium and cervix are found after these diagnostic procedures have been carried out, the patient should be carefully observed. If the bleeding recurs, pelvic exploration with hysterectomy and/or removal of the adnexa as indicated is usually preferred. This offers a final means of excluding organic pathology either uterine or adnexal which may still be present even though the previous diagnostic studies were negative.

Repetitious bleeding or the so-called bloody menopause probably bears some relationship to future endometrial cancer. The patient with a cancer phobia

is severely disturbed by such irregular uterine bleeding, at an age when women know the bleeding is definitely abnormal. This can be eliminated by hysterectomy.

### Summary

Two hundred twenty-two patients, 40 to 56 years of age, excluding postmenopausal women, were admitted with a diagnosis of "functional uterine bleeding—cause undetermined."

There were no cases of endometrial hyperplasia in the younger age group.

Atypical endometrial hyperplasia was found in 17 of the older patients. Six patients in this group had associated adenocarcinoma.

Progestational endometrium was found in 25.8 per cent of the older women, as compared to 21 per cent of those under 35 years of age. MacKay and associates have shown that the early stages of endometrial cancer bear a histochemical resemblance to progestational endometrium, which might indicate that there may be a progesterone-like hormone acting in the genesis of endometrial carcinoma. The incidence of organic pathology as a likely cause of bleeding was 30.2 per cent.

Unsuspected malignancy occurred in 4.5 per cent.

### References

1. Jacobs, W. M., and Lindley, J. E.: *AM. J. OBST. & GYNEC.* 71: 1322, 1956.
2. Novak, Edmund R.: *AM. J. OBST. & GYNEC.* 71: 1312, 1956.
3. McKay, D. G., Hertig, A. T., Bardawil, W., and Velardo, J. T.: *Obst. & Gynec.* 8: 140, 1956.
4. Clyman, M. J.: *Obst. & Gynec.* 6: 258, 1955.

### Discussion

DR. A. W. DIDDLE, Knoxville, Tenn.—Drs. Wall and Jacobs indicate that, given a group of women 40 years old or more with apparent dysfunctional uterine bleeding, some will prove to have endometrial hyperplasia or other anatomical genital disease as determined by histological study. In some instances the hyperplasia will be atypical with neoplasia. On the contrary, given a group of women less than 40 years old with dysfunctional uterine bleeding, clinically atypical endometrial neoplasia is unlikely.

The demarcation of age 40 is described in studies concerning endometrial carcinoma. Taylor and Becker recorded 531 women with this disease. Most were more than 40, none was under 30, and there were a few 30 to 40 years old. Likewise Randall and Goddard observed that this disease was infrequent under the age of 40 but did record 2 cases in women less than 30.

Atypical endometrial hyperplasia as a precursor of adenocarcinoma of the endometrium has been stressed by many, including Halban, Scheffey, Hertig, Gusberg, Emil and Edmund Novak, Rutledge, Brewer, and others. The opinion is strengthened by bizarre endometrial patterns occurring together, such as benign atypical and malignant hyperplasia. In addition, gradual transition in the endometrium from a benign to a neoplastic condition has been observed within the same patient over a period of years.

O'Connor and I reviewed the case histories of 50 consecutive patients hospitalized with a tentative diagnosis of dysfunctional uterine bleeding and treated personally. None had fibromyomas. They ranged in age from 40 to 56 years. Ten of the 50 proved to have endometrial hyperplasia. The rest had either proliferative, secretory, menstrual, or mixed endometrial patterns. A hysterectomy was performed on one of the 10 women. An incidental finding included a small thecoma in each ovary in this instance. Another patient had atypical hyperplasia with adenocarcinoma. This woman had been treated

by curettage eight months previously with a diagnosis of benign endometrial hyperplasia. Whether or not the endometrial hyperplasia was a precursor of the neoplasm or the true diagnosis was missed at the time of the first curettage is questionable. This experience shows the need, however, to follow the patients who have recurrent symptoms. One curettage or smear may fail to provide an accurate diagnosis. In some instances another thing happens—adequate sampling of the curettings is not made.

Among nearly 100 other women less than 40 years old and with dysfunctional uterine bleeding clinically, we found one with atypical endometrial hyperplasia, a second with early endometrial adenocarcinoma, and a third with carcinoma in situ of the cervix plus stromal hyperplasia of the ovaries.

We were privileged to see the patient with adenocarcinoma with Drs. Lambeth and Kintner. They recently gave their experience in a case report. They emphasized the problems of making an anatomical diagnosis and of clinical management. Their patient was 30 years old. She had been studied repeatedly with endometrial biopsies since the age of 15 years when the first diagnosis of endometrial hyperplasia was made. A hysterectomy was done at age 30 years, admittedly on a divided opinion from at least a half dozen experienced pathologists. The majority believed that early adenocarcinoma was present in tissue removed shortly before the hysterectomy was done. Others were of the opinion that the tissue was atypical but benign.

In conclusion, it is my experience that most women with dysfunctional uterine bleeding who are over 35 years old should usually have the benefit of a diagnostic curettage. If abnormal bleeding is persistent even those under 35 should have the procedure. If the patient proves to have atypical endometrial hyperplasia as defined by the essayists then one should keep in mind that this kind of woman may develop other abnormal endometrial patterns later in life.

DR. GILBERT F. DOUGLAS, Birmingham, Ala.—A few years ago we studied 106 cases of what we termed our "bleeding clinic," getting from 1 to as many as 13 biopsies from each patient of this group, endeavoring to study the type of endometrium at weekly intervals. It was rather interesting to find that we had identical percentages of patients with secretory and proliferative endometrium, steadily. Three cases of malignancy, 2.8 per cent, were picked up where we had not previously suspected malignancy. We concluded that, if we were to accomplish anything, these cases should be studied intensively, whether in the private office or in the clinic. We felt it was our obligation to follow through.

I was interested in Dr. Wall's cases, in which approximately two to one were in the proliferative stage. Was that correct?

DR. IRVING F. STEIN, Chicago, Ill.—I think we get mistaken ideas from the essayist and the official discussant to the effect that there is a definite age at which we should look for adenocarcinoma of the uterus. Carcinoma can occur, of course, at any age.

Dockerty of the Mayo Clinic and Fair from Columbia University reported a group of endometrial carcinomas in women from 19 to 40 years of age, and there was a considerable number of patients in the younger age group studied. I do not think you should specify 40, or 35, as the time to look for carcinoma.

All these cases of bleeding should be investigated for the possibility of endometrial carcinoma.

DR. WALL (Closing).—Dr. Stein, we are certainly not emphasizing any particular age at which you should look for carcinoma. I am glad you stressed that point, because I think every doctor should have "cancer on the brain."

Adequate sampling in the curettage might make for some differences in interpretation and diagnosis; that certainly accounts for some of our mistakes.

The study of the incipient histological neoplastic changes that gynecologists and gynecological pathologists carry on is very commendable, because it may well be the key that is going to turn the lock that may tell us a little bit more about the endocrine tie-up with the development of neoplasia.

## OBSERVATIONS ON METACHROMATIC GRANULES IN HUMAN ENDOMETRIUM\*†

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**A**BNORMAL uterine bleeding is one of the more frequent gynecologic complaints. The most important consideration in a patient with this problem is an accurate determination of the cause. This, in turn, should be followed by a selected course of indicated therapy. Far too often normal organs are sacrificed by surgery or rendered functionless by x-ray because of persistent symptoms following inadequate treatment.

In 1947, Allen and his associates<sup>1</sup> described a condition of abnormal bleeding tendencies related to an excess of a circulating anticoagulant, most likely heparin or a heparin-like substance. A method was described to measure its presence titrametrically—the protamine titration. In 1949, an increase of this anticoagulant during menstruation and in certain cases of menorrhagia was reported.<sup>6</sup> The effectiveness of protamine sulfate and toluidine blue in neutralizing the anticoagulant, reversing the bleeding symptoms, and returning the protamine titration to normal was demonstrated.

In 1951, one of us (W. L. R.) reported on the use of toluidine blue and protamine sulfate in treating abnormal uterine bleeding.<sup>11</sup> The results in 25 cases of menometrorrhagia treated with toluidine blue were described and compared with 46 cases treated by the usually accepted methods. Eighty per cent of the patients who received toluidine blue experienced partial or complete relief of bleeding symptoms. These results were much better than those obtained in the 46 control cases treated by other means. Since then other investigators have made similar observations with comparable results<sup>4, 5, 8</sup> (Table I).

TABLE I. REPORTS ON TREATMENT WITH TOLUIDINE BLUE

AUTHOR	DATE	NUMBER OF CASES	CONTROL	RESULTS		
				GOOD	FAIR	NONE
Allen <sup>1</sup>	1949	41	Protamine titration	27	7	7
Elghammer <sup>6</sup>	1949	51	Protamine titration	31	10	10
Rumbolz <sup>11</sup>	1952	25	Protamine titration	12	7	6
Lathrop <sup>8</sup>	1952	63	None	43	15	5
Chesley <sup>5</sup>	1953	49	Protamine titration	26	13	10
Bickers <sup>4</sup>	1953	36	Protamine titration Curettage	11	3	22

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Of particular interest is the report of Bickers<sup>4</sup> who used curettage specimens in conjunction with protamine titration in studying the effectiveness of toluidine blue in the treatment of abnormal uterine bleeding. Forty-two patients in this report received toluidine blue, but the best results were obtained in cases of cyclic hypermenorrhea associated with normal ovulation, normal secretory endometrium, and an elevated protamine titration. Fifteen of the cases were diagnosed as hypermenorrhea associated with normal ovulation. In 9 of these there was an elevated titration and in all but one a return of normal menses was experienced with treatment. In 3 of 8 cases of hypermenorrhea associated with a proliferative endometrium there was an elevated protamine titration and also improvement on toluidine blue, while the other cases showed no change. No significant effect was noted in the cases of polymenorrhea.

Each investigator has made his report with varying degrees of enthusiasm or skepticism, but none has adequately explained just why toluidine blue works. Originally<sup>1</sup> it was felt that the action was one of neutralizing an abnormal excess of the circulating anticoagulant, most likely heparin; but no explanation as to the origin of this anticoagulant was offered.

Recently, Latta and Beber<sup>9</sup> described the presence of cells containing metachromatic eosinophilic granules in the core of villi of the human placenta. These cells were thought to be mast cells, and it was believed that the metachromatic granules were the source of heparin in the placenta, which, when mixed with intravillous blood, rendered it incoagulable. It was further suggested that similar cells in endometrium could serve as a source of locally available heparin which mixes with menstrual blood and produces free bleeding. This possibly offered a rationale for antiheparin drugs such as toluidine blue in treating certain cases of menorrhagic bleeding. With this in mind, an investigation was undertaken to examine human endometrium for the presence of cells containing metachromatic granules in their cytoplasm. A correlation of the presence and numbers of these cells in the different stages of normal menstruation was made. Similar studies were undertaken on the endometrium from patients with abnormal uterine bleeding.

### Material and Methods

Fresh surgical specimens were obtained by curettage or hysterectomy. Only a representative piece of tissue was used in this study, the remainder being sent through the routine channels for histologic diagnosis. The selected tissues were fixed in lead acetate, blocked, mounted, and stained with toluidine blue. To compare our results, a portion of the cases were also studied with the use of chloroacetyl ester stains described by Gomori.<sup>7</sup> The histologic specimens were stained by a routine hematoxylin and eosin method. One hundred and nine specimens were collected, examined, and correlated in this study. The count of the number of cells present in any one specimen was made independently by two different individuals and their results compared. An exact determination of the number of cells in a section of endometrium is practically impossible. It has therefore been necessary to approximate the number of cells, grading them from zero to three plus by the number seen per high-powered field. Five or more fields were examined on each specimen

before an approximation of the number of cells was attempted. One to three cells per high-powered field was graded as one plus, four to six cells per high-powered field as two plus, and seven or more cells per high-powered field as three plus.

### Results

Of the 109 cases studied in this report, 103 were in the usual menstrual years, 3 were in the 50 to 60 year age group, and 3 were in the group more than 60 years of age. Twenty-four cases were considered to be normal from the standpoint of menstrual history, the endometrium being obtained as a biopsy in an infertility workup. Thirty-five cases were clinically diagnosed as cyclic hypermenorrhea with a history of an increase in the amount or duration of menstrual flow. Thirty-nine cases were diagnosed as polymenorrhea with the menstrual flow occurring too frequently. Ten patients were pregnant, the tissue being obtained at the time of the evacuation of the uterus following spontaneous abortion. One patient had a histologic diagnosis of adenocarcinoma of the endometrium.

Of the 24 cases clinically considered as normal, 15 had a histologic diagnosis of secretory endometrium, 4 of proliferative endometrium, and 5 of an atrophic endometrium. In the 35 cases of hypermenorrhea, 32 had a secretory-phase endometrium and only 3 had a proliferative phase. In the 39 cases of polymenorrhea, 33 had a proliferative-phase endometrium and only 6 a secretory phase.

TABLE II. NUMBER OF CELLS WITH METACHROMATIC GRANULES IN ENDOMETRIUM

SYMPTOMS AND FINDINGS	NUMBER OF CASES	CELLS*			
		0	1+	2+	3+
Normal Menstruation (24 cases)					
Secretory endometrium	15	2	5	7	1
Proliferative endometrium	4	1	3		
Atrophic endometrium	5	4			1
Hypermenorrhea (35 cases)					
Secretory endometrium	32		7	10	15
Proliferative endometrium	3			2	1
Polymenorrhea (39 cases)					
Secretory endometrium	6		4		2
Proliferative endometrium	33	11	15	3	4
Pregnancy (10 cases)	10		1	1	8
Adenocarcinoma (1 case)	1				1

\*1+ = one to three cells per high-powered field.

2+ = four to six cells per high-powered field.

3+ = seven or more cells per high-powered field.

All cases with metachromatic granules in this series were graded zero to three plus according to the presence and number of cells, as described earlier. The clinically normal group of cases with secretory endometrium showed one, two, or three plus cells in 13 of the 15 cases, while only 2 showed no cells. The normal cases with proliferative endometrium showed one plus cells in 3 instances and none in the fourth. One of the cases with atrophic endometrium showed three plus cells while the remaining 4 showed no cells. The case with three plus cells was associated with endometrial polyps. Four of the entire series of cases were associated with endometrial polyps and all were graded three plus.

Fig. 1.

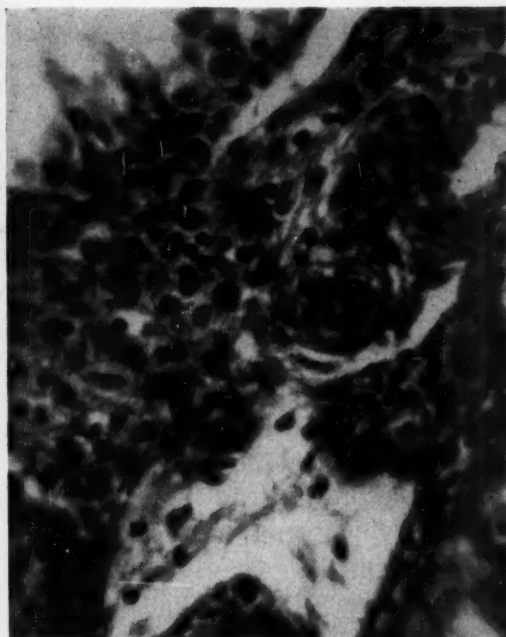


Fig. 2.

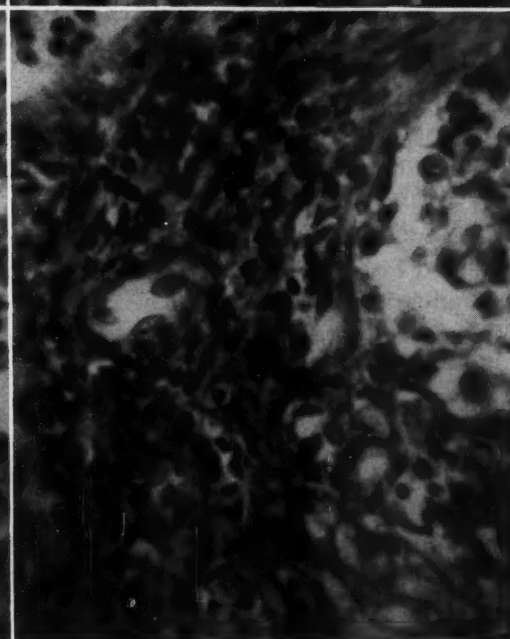
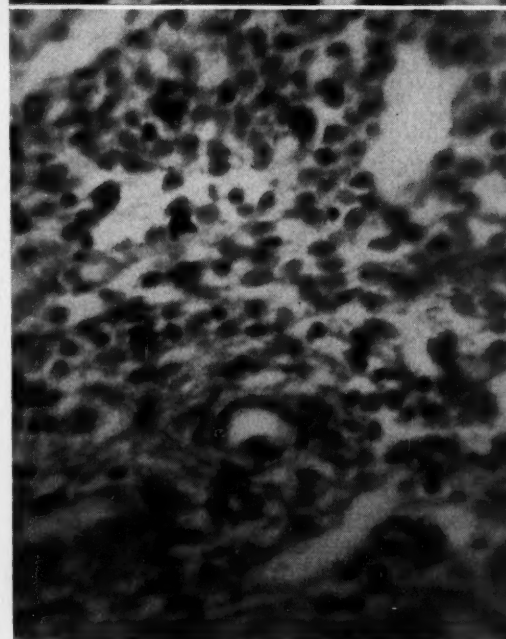
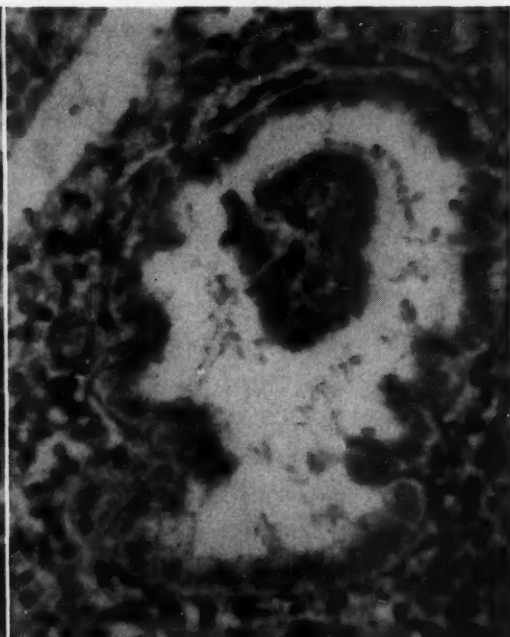


Fig. 3.

Fig. 4.

Fig. 1.—Clinical diagnosis of hypermenorrhea. Histologic diagnosis of late secretory endometrium. Graded 3+ cells. ( $\times 450$ ; reduced  $\frac{1}{6}$ .)

Fig. 2.—Clinical diagnosis of hypermenorrhea. Histologic diagnosis of mid-secretory endometrium. Graded 3+ cells. ( $\times 450$ ; reduced  $\frac{1}{6}$ .)

Fig. 3.—Clinical diagnosis and histologic diagnosis of early abortion. Graded 3+ cells. ( $\times 450$ ; reduced  $\frac{1}{6}$ .)

Fig. 4.—Clinical and histologic diagnosis of adenocarcinoma of endometrium. Graded 3+ cells. ( $\times 450$ ; reduced  $\frac{1}{6}$ .)



All of the 35 patients with diagnoses of hypermenorrhea showed metachromatic granule-bearing cells in the endometrium. Twenty-eight cases were graded as two or three plus and only 7 were graded as one plus. The 3 cases of proliferative endometrium in this group also showed two and three plus cells.

The 39 cases of polymenorrhea showed far fewer cells than the preceding group. Thirty cases were graded as zero or one plus and only 9 were considered as two or three plus. Three of these 9 cases had a histologic diagnosis of endometrial polyps.

In the pregnancy group 8 of the 10 patients were graded as three plus. The case of adenocarcinoma of the endometrium showed an abundance of granule-bearing cells and was graded as three plus (Table II).

### Comment

The presence of metachromasia, mast cells, and cells with metachromatic eosinophilic granules in their cytoplasm have been described in endometrium and in other tissues of the body.<sup>3, 10, 12, 13</sup> There is some difference of opinion as to the occurrence and importance of these findings in endometrium. Authorities generally agree, however, that the metachromatic granules represent heparin.

Asplund and Holmgren<sup>3</sup> studied human endometrium and described a particular type of cell which contained metachromatic granules. These cells were called "specific cells" and were pointedly differentiated from tissue mast cells by the authors. An increase in the so-called "specific cells" during the secretory phase of the normal menstrual cycle was observed. An increase was also shown in pregnancy and certain pathologic conditions of the endometrium. Mast cells apparently made no consistent change throughout the menstrual cycle in their observations.

McKay<sup>10</sup> demonstrated a stromal metachromasia in endometrium which seemed to be more marked in the proliferative phase of the cycle, disappearing around the time of ovulation and reappearing in the late secretory phase. In this report mast cells were found during the proliferative phase of the cycle, they diminished in number in the early stage of secretion, and reappeared in moderate numbers during the late secretory phase. Other investigators<sup>12</sup> have likewise described tissue mast cells in the endometrium which increase in number during the secretory phase of the cycle.

Our findings of cells with metachromatic eosinophilic granules in their cytoplasm are consistent with these reports. The cells occur sparsely in the proliferative phase of the cycle and increase during the progesterone-stimulated secretory phase. Cases of hypermenorrhea associated with secretory endometrium showed greater numbers of cells than were found in normal cases at the same stage of the cycle. Pregnancy also showed increased numbers of cells. The cases of polymenorrhea associated with proliferative endometrium showed far fewer cells.

Gomori<sup>7</sup> described chloroacyl ester stains which he feels are specific for mast cells. This staining technique was used on a number of the specimens and the findings compared with toluidine blue stain on the same specimens.



The grading in regard to the number of cells found was comparable in the cases studied. We believe that the cells containing metachromatic granules are tissue mast cells and feel that the granules are heparin. This readily available source of heparin in endometrium when increased in amount can explain certain cases of heavy or prolonged menstrual bleeding associated with secretory endometrium. Marked increases of this anticoagulant can be demonstrated by an elevated protamine titration. Lesser degrees of heparin excess can cause a local effect with increased uterine bleeding and still not produce systemic manifestations. It seems that antiheparin drugs have a direct neutralizing effect on increased numbers of heparin-bearing granules in mast cells. Histologic evidence and clinical response indicate that toluidine blue is of greatest value in cases of cyclic hypermenorrhea associated with normal ovulation and normal secretory endometrium. Little or no response can be demonstrated in cases of organic disease even though the numbers of mast cells appear to be increased in certain instances. Wherever feasible, a protamine titration is a valuable adjunct to effective therapy. Before treatment is instituted, care must be exercised to rule out the presence of an unsuspected malignancy.

### Conclusions

Selective staining of endometrium demonstrates the presence of cells with metachromatic eosinophilic granules in their cytoplasm. These cells are tissue mast cells and the granules are heparin. There is an increase in number of mast cells from the time of ovulation throughout the secretory phase of the cycle. Mast cells are also increased in pregnancy and certain bleeding states associated with a secretory endometrium.

We wish to thank Dr. Miles Foster and Dr. John Latta for their cooperation and encouragement. We wish to acknowledge the interest and services of Miss Angeline Koelling and Miss Jan Sullivan in our laboratories.

### References

1. Allen, J. Garrot, Borgardus, George, Jacobson, L. C., and Spurr, C. L.: *Ann. Int. Med.* 37: 371, 1947.
2. Allen, J. Garrot, Grossman, Burton J., Elghammer, R. M., Moulder, Peter V., McKean, C. L., Jacobson, L. C., Pierce, M. Smith, T. R., and Crosbie, James M.: *J. A. M. A.* 139: 1251, 1949.
3. Asplund, J., and Holmgren, H.: *Acta anat.* 3: 312, 1947.
4. Bickers, William: *AM. J. OBST. & GYNEC.* 66: 1313, 1953.
5. Chesley, Ray F., Padovano, Joseph, Head, Thomas F., and Leving, Martha: *Bull. Margaret Hague Maternity Hosp.* 6: 100, 1953.
6. Elghammer, Richard M., Grossman, Burton J., Koff, Arthur, Moulder, Peter V., and Allen, J. Garrot: *Surg., Gynec. & Obst.* 89: 764, 1949.
7. Gomori, G.: *J. Histochem.* 1: 469, 1953.
8. Lathrop, C. A., and Carlisle, W. T.: *AM. J. OBST. & GYNEC.* 64: 1376, 1952.
9. Latta, John S., and Beber, Charles: *Science* 117: 498, 1953.
10. McKay, Donald G.: *AM. J. OBST. & GYNEC.* 59: 875, 1950.
11. Rumbolz, W. L., Moon, C. F., and Novelli, J. C.: *AM. J. OBST. & GYNEC.* 63: 1029, 1952.
12. Sylven, B.: *Exper. Cell. Research* 2: 252, 1951.
13. Wislocki, G. B., and Dempsey, E. W.: *Am. J. Anat.* 83: 1, 1948.

### Discussion

DR. E. G. HOLMSTROM, Salt Lake City, Utah.—The patient with cyclic menorrhagia in whom no local lesion of the uterus such as a submucous myoma, or systemic disease such as a blood dyscrasia can be demonstrated presents one of the more difficult therapeutic problems. Our experience, like that of the authors, has been that some of these patients will benefit by the administration of toluidine blue, others will not.

The authors have tried to demonstrate that, in those who can be expected to benefit from the administration of toluidine blue, the endometrial connective tissue will show an increased number of cells with metachromatic granules. They assume that the cells containing the metachromatic granules are the source of a heparin-like substance which is responsible for the increased bleeding. This appears at first glance to be a logical assumption, for it has been well shown by many workers in this field that these metachromatic granules contain heparin or heparin-like substances. It has also been demonstrated, however, at least in some animals, that the presence of increased numbers of mast cells with metachromatic granules is not necessarily associated with anticoagulative activity. Oliver, Bloom, and Mangieri,<sup>1</sup> working with mast cell tumors in dogs, found that, although these tumor mast cells contained large amounts of heparin and were present in great numbers in the blood stream, these animals exhibited no evident disturbance in the coagulability of the blood. Some investigators would say that the granules are sites in which the heparin-like substance is stored. In order for this substance to provide an anticoagulative effect, the mast cells would have to disintegrate and release the material in the local area. Some support for this concept is derived from the work of Dougherty and Higginbotham in our Department of Anatomy. They have shown that the administration of some noxious stimulus to these cells results in the shedding of the granules which are then ultimately taken up by surrounding fibroblasts. It may be that the shedding of the granules results in the liberation of some of the contained heparin-like substance in the area and, therefore, interferes with normal coagulability. The administration of the toluidine blue may neutralize this substance and thereby render it inactive. If this is the mechanism of action by which the toluidine blue therapy is effective, one might expect that, during the time of active bleeding, free granules might be demonstrated in the endometrial connective tissue. Therefore, I wish to ask Dr. Rumbolz whether or not the patients studied were bleeding at the time of the endometrium was obtained.

I have two additional questions. Have any endometria been studied before and after the administration of toluidine blue? If so, was there any difference in the numbers of mast cells found? Also, is there any correlation between the number of mast cells present and the response to treatment with toluidine blue?

To me, this study has a much wider importance than the demonstration of some apparently specific change in the endometrium in some cases of menorrhagia. Studies such as this one may also aid in clarifying the basic mechanism responsible for bleeding during the normal menstrual cycle. We know that withdrawal of estrogen or progesterone will result in bleeding. Bleeding is associated with some recognizable changes in the endometrial vascular bed. We still do not know the nature of the chemical change which occurs in the endometrial connective tissue secondary to the hormone withdrawal. When this mechanism has been clarified, we will then be able to explain why the vascular changes take place. It seems very likely that further study of these intriguing granules will provide the answer.

Drs. Rumbolz and Greene are to be congratulated on their auspicious start in the elucidation of this question. We hope that they will continue their studies.

### Reference

1. Oliver, J., Bloom, F., and Mangieri, C. N.: *J. Exper. Med.* 86: 107, 1947.

DR. J. MILTON SINGLETON, Kansas City, Mo.—In 1934 Dr. Russell Hayden reported, with me, a number of cases of menometrorrhagia with achlorhydria, and he classed this

as achlorhydric anemia with menorrhagia. In the future I certainly intend to watch cases that I consider in this class for granules as described by Dr. Rumbolz.

DR. RUMBOLZ (Closing).—I certainly am the first to admit that neither the presence of increased numbers of metachromatic granules nor the administration of toluidine blue is the present-day solution to this maze of abnormal bleeding problems.

Only recently a few investigators have attempted to delve into the uterine bleeding problem from a histochemical point of view. For too long we have been blocked by limited clinical description of the symptoms and an incomplete histologic interpretation of the tissue in making our diagnosis. The two are often completely divorced from each other.

Dr. Holmstrom has nicely demonstrated the granules which contain heparin or heparin-like substance. It has been shown that the number of granules will often determine the heparin yield of a given tissue.

He has also pointed out that in vivo changes of anticoagulant activity were not apparent, even though increased numbers of mast cells occurred. In the same cases, however, very marked anticoagulant activity could be demonstrated in the in vitro studies, and a yield of heparin could be obtained that would change the test tube coagulation of the blood.

In almost all the cases studied, the tissues were obtained on or near the first day of menstruation. Efforts were made to obtain tissues near the late phase of the cycle.

Dr. Holmstrom asked if any endometria had been studied before and after the administration of toluidine blue, and, if so, if there was any difference in the number of mast cells found. A number of cases in the series clinically diagnosed as hypermenorrhea did receive routine therapy with satisfactory clinical response. It was our impression, in studying these cases, that fewer cells were found, with more scattering of the cases into the one- and two-plus range, as we saw in the normal group. However, with the admittedly inaccurate determination of number of cells, no satisfactory conclusions were possible.

No direct correlation between the number of cells present and the response to toluidine blue therapy was attempted. Cases of hypermenorrhea with elevated protamine titration showed many more mast cells and gave the best clinical response to the administration of toluidine blue, however.

I am not familiar with Dr. Singleton's report. It proposes some intriguing thoughts, because mast cells are present in the stomach mucosa in tremendous numbers, and it makes you wonder a little bit about the situation.

## OVARIAN FUNCTION AND WOMAN AFTER THE MENOPAUSE\*

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ALL will agree that estrogens affect many tissues of the body. No one denies that the ovary continues to produce hormone after the menopause, but the amount of postmenopausal function varies considerably among individuals. No one denies that the advantages of postmenopausal function are not evident at this time. All will agree, however, that at times both ovaries should be removed. No one denies that removal of both ovaries terminates ovarian function, nor that removal of the ovaries means castration of the individual.

No one believes that castration, by whatever means, can be expected to improve a woman's appearance. Nor does anyone believe that removal of both ovaries assures longer life, though many might testify that castration has made their lives seem longer.

We cannot consider this subject until we define the menopause. Rogers,<sup>8</sup> in a recent and most informative discussion of the subject, simply defines the menopause as "that time in a woman's life when she ceases to menstruate and can no longer conceive."

To me it has seemed difficult to consider the advisability of preserving ovarian function after the menopause, without feeling obliged to defend my point of view to the extent of at least questioning the rationale of the prophylactic removal of ovaries, and attempting to justify their preservation when laparotomy is indicated during the climacteric.

Opinions regarding the advisability of preserving the ovary in younger women vary only in degree, whereas opinions regarding the advisability of preserving the ovary after the menopause are widely divergent. Many surgeons and some gynecologists believe that the ovary is of no value to the woman after her menopause. Many advise the incidental removal of both ovaries whenever laparotomy is indicated, any time after the woman has "had her family." Now that hysterectomy has become the most frequent indication for pelvic laparotomy, this practice has become a matter of considerable importance. The ovaries, like the appendix, are now frequently removed "incidentally," "routinely," or "prophylactically."

Few tissues in the body are favored by such a zeal for prophylactic surgery as is the ovary. Those who minimize the importance of ovarian function after the menopause seem to liken the ovary to the umbilical cord—all important for a time and then regarded only as a vestigial reminder of the time when it was indispensable.

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The risk of preserving the ovary after the menopause is well known. The ovary is a fairly frequent source of neoplasia, and if preserved at the time of an indicated laparotomy during the climacteric, either ovary may at some later date be the source of a tumor requiring another laparotomy. An even greater danger is the risk of ovarian malignancy. All will admit that the risk of preserving the ovary is at least equal to the incidence of ovarian carcinoma. On the other hand, the advantages of preserving the ovary after the menopause are not well established, and much of the argument obviously stems from preconceived notions, prejudice, or sentiment.

Emge<sup>5</sup> has suggested that the five most common arguments cited for the "incidental" removal of normal ovaries are: (1) It eliminates the chance that cancer will eventually develop in the ovary. (2) The function of the ovary is negligible after the menopause. (3) Since even benign neoplasms of the ovary may develop after the menopause, why expose the patient to the possibility of another operation when it is so convenient to remove the ovaries when the abdomen is open? (4) Why not remove the ovaries, when substitution therapy is so readily available, inexpensive, and so efficient? (5) Removal of ovaries does not usually involve a significant degree of psychological disturbance.

It seems to me that we can do no better than to follow Emge's outline. Certainly we would all at first admit concern regarding the possibility that ovaries, or one ovary, preserved at the time of an indicated laparotomy, may later become the source of a rapidly fatal neoplasm. The statistical chance that any woman will develop a carcinoma of the ovary seems pretty well established.

If we are to take into consideration the frequency or risk of malignancy, we must keep clearly in mind the distinction between two figures which indicate the magnitude of the cancer problem. The first is the *annual incidence rate*, which expresses the number of new cases of a specific type of malignancy that can be expected to develop each year per unit of the population. A second figure expresses the *probability* of any single individual developing a malignancy during the remaining years of his or her life. The latter figure obviously must take into account the individual's age, probable length of life, and the annual incidence rate for each year the individual may be expected to live.

In the state of New York, exclusive of New York City, cancer has been a reportable disease since 1940. During the past ten years, the reporting of cancer to the Bureau of Cancer Control<sup>3, 4</sup> has become so universally practiced we believe that the figures are now accurate and reliable. They are based upon the number of cases reported during the years 1949, 1950, and 1951, among an Upstate New York population which, according to the 1950 census, included approximately two and one-half million adult women.

It seems practical to keep in mind the relative risk of ovarian cancer and carcinoma of the breast in the age groups most frequently considered. Between the ages of 20 and 25 years, for instance, we should expect to find an average of one case of cancer of the breast and one of cancer of the ovary per 100,000 women per year. Between the ages of 25 and 29, we should expect to find 5 malignancies of the breast and 2 carcinomas of the ovary per 100,000 women per year. The risk of malignancy in the breast increases rapidly as women grow older. It is five times more likely than ovarian malignancies in the thirties, and six times as frequent in the forties. In the fifties, when carcinoma of the ovary is most frequent, the ratio is again 4 carcinomas of the

breast per one carcinoma of the ovary. After 60 the relatively greater frequency of malignancy in the breast continues, whereas the risk of ovarian malignancy decreases noticeably as women grow older.

Expressed in terms of new cases that could be expected to develop within a given population, in any one year, it might be well to remember that we should not expect to find more than two new cases of ovarian malignancy per year among each 10,000 women in the community.

Though such figures regarding the annual incidence rate are of considerable interest to public health officials and those interested in the development of cancer detection services, they are of little interest to the patient or her doctor. Both are more concerned with the individual woman's chance of developing cancer between her present age and the termination of her life expectancy. Estimations of the lifetime probability of any woman developing ovarian malignancy are also of greater value to us at the moment than are figures indicating that every woman now faces a 3 in 20,000 (13.90 per 100,000) chance of developing ovarian malignancy within the next calendar year.<sup>3, b</sup>

Every girl reaching voting age faces the lifetime probability of slightly less than one (0.993) chance in 100 of some day developing a malignancy of the ovary. That probability remains at 0.9 plus per cent until the woman reaches her forty-fifth year, after which it begins to decline. At 50 the probability is 0.82 per cent; after age 55, 0.7 per cent; after 60, 0.6 per cent; after 70, 0.3 per cent. In comparison, women still face a 5 per cent chance of developing a malignancy of the breast after their forty-fifth year and that chance still approximates 3 per 100 among women over 75 years of age. Again, it is obvious that the risk of any woman developing a malignancy of the breast is five times as great at 45 years and ten times as great among women 75 years of age as the risk of ovarian malignancy.

We might also remember that, when we take mortality figures into consideration, it becomes evident that 2 of each 3 women who develop a malignancy of the breast will probably die of their neoplasm in less than five years, whereas only one-tenth to one-fifth of the women who develop a malignancy of the ovary will survive an appreciable length of time. Combining the previously quoted figures regarding probability and these mortality estimates it becomes evident that the probability that any woman's death will be due to malignancy of the breast approximates 1.65 per cent, whereas the lifetime risk of death due to ovarian malignancy is approximately half of that figure, i.e., 0.81 per cent.

Emge<sup>5</sup> seems to disagree with those who feel that ovarian function after the menopause does not justify preservation of the ovary.

Acknowledging an apparently general impression that estrogen production ceases with the menopause, Struthers<sup>10</sup> recently observed that opinions seem to be changing, that many now believe that in a good many instances estrogenic activity continues for years after the menopause. Expressing surprise that so little has been done "to exchange such generalizations for something more precise," he reports an attempt to carry out an investigation designed to (1) determine the number of women in whom postmenopausal estrogenic activity was present, (2) make a quantitative estimate of that estrogen, and (3) determine its source.

Struthers employed vaginal smears as a means of estrogen determination, following Aeppli and Rosenmund's<sup>1</sup> suggestion that the smear method has certain practical advantages over the biological assays of Allen.<sup>2</sup> Since other studies had indicated that the two methods gave remarkably similar results, Struthers concluded that the cytologic methods could therefore be regarded as sufficiently accurate for his purpose. Smears were graded from

389 patients. All who admitted taking estrogens or androgens in any form by any route were excluded. Struthers concluded that 53.2 per cent evidenced considerable estrogenic activity after the menopause, that the presence of some estrogen was indicated in 26.6 per cent, and that in only 20.1 per cent no estrogen was present.

Struthers' figures could certainly be verified in the office practices of many clinicians. We have noted that well over 50 per cent of postmenopausal women exhibit a good estrogen effect in their vaginal smears, taken routinely as a cancer detection measure. Moreover, as our patients grow older, only about 15 per cent seem to develop atrophic changes to a degree causing symptoms. Struthers noted, however, that the proportion of women without ovaries who evidenced a substantial degree of estrogenic activity was only 14.5 per cent less than was shown by women with apparently normal postmenopausal ovaries. This observation led him to suspect that the amount of estrogen produced by postmenopausal ovaries might be insignificant.

To discover whether the adrenals were the source of estrogen in postmenopausal women, Struthers thought it advisable to examine the vaginal smears of women whose ovaries and adrenals had been removed. Eight such cases became available to his study, but one patient died within 24 hours after adrenalectomy. In 4 of the remaining 7 an estimate of estrogen production was made before and after adrenalectomy. In 3 there was no change in the estrogen level and in the fourth there was a slight reduction. Of the 3 whose level remained unchanged, 2 showed high and one a low level of estrogenic activity. If any conclusions may be drawn from so small a series, it suggests that the ovaries and the adrenals are not the only sources of postmenopausal estrogen.

Other steroids are probably implicated, but considerable evidence does suggest the beneficial effects of estrogen on the skin as well as upon buccal, nasal, and genitourinary membranes. Even more important is the fact that a lack of estrogen favors the development of osteoporosis and atherosclerosis.

Griffith<sup>6</sup> has recently called our attention to the evidence that women who had undergone bilateral oophorectomy were later found to have developed, by the age of 50, a degree of coronary atherosclerosis not noted among controls until they had passed their seventieth year. Decade by decade, the incidence of severe coronary atherosclerosis was between 10 and 45 per cent greater in the oophorectomized women than in those regarded as controls.

The fear that estrogens, long unopposed, due to anovulatory cycles, or as used in prolonged therapy, might be carcinogenic in human beings does not often seem evidenced in clinical experience. Many have long suspected that preservation of ovarian function maintains a histologic background essential to the eventual development of breast and endometrial carcinoma. Such circumstantial evidence is not universally accepted, however, and continues to stimulate endless controversy. It is evident that adenocarcinoma of the endometrium may develop without preceding persistence of anovulatory cycles and an uninterrupted stimulus by estrogen. There is also a lack of evidence that malignancies of the breast are more frequent among women whose ovarian function persists to a later than average age.

At this time we can only conclude that women whose ovarian function persists years beyond the average age of the menopause seem to grow older more slowly, and perhaps more gracefully. There is but little evidence that such women are predisposed to a significantly greater incidence of malignant disease as the result of a later menopause, and even less to suggest that they would have benefited by prophylactic castration at a younger age.



Why preserve the ovary at the time of an indicated laparotomy, if there is a good chance that it will later develop a neoplasm requiring another laparotomy? For some years my answer to the third argument Emge lists has been based upon purely clinical experience. Whenever a benign-appearing cystoma seems unilateral, we have found that the chance of bilateral occurrence requires careful inspection, palpation, and bisection of the opposite ovary. We have not been convinced that such an "other ovary" need be removed, if it appears entirely normal, simply because the chance of its involvement by any type of neoplasm at a later date seems to be less than 3 per cent. This management is also based upon belief that the usual pathogenesis of ovarian neoplasia justifies the assumption that by the time one ovary has developed a tumor large enough to indicate laparotomy, it is unlikely that a similar or other neoplasm will begin in an opposite ovary which shows no evidence of neoplasia on bisection.

We must admit, however, that it might be said of this currently mature generation that in our hands pelvic laparotomy has become so "safe" a procedure that the lack of pathology in the tissues removed provides some of the problems of our time.

An apparently general willingness to remove ovaries when only dysfunctional states or no abnormality is found at laparotomy is a problem that has been adequately discussed and condemned by Norman Miller,<sup>7</sup> James Doyle,<sup>4</sup> and many others. The advisability of attempting to preserve as much ovarian tissue as possible when we recognize that ovarian disease is benign, is not within the scope of the present discussion. Aside from the moral and ethical considerations implied in that oft-repeated phrase "unnecessary surgery," we are attempting to emphasize, however, that there may be advantages to be realized when a woman is allowed to keep her ovaries.

Emge's fourth point is probably the argument most frequently given as evidence that prophylactic oophorectomy is advantageous, harmless, and practical. Since there is only a 1 per cent chance that any woman will develop carcinoma in normal ovaries, when hysterectomy is indicated and the woman is approaching the time of the menopause, why preserve ovaries, say the advocates of prophylactic oophorectomy. Is it not true that estrogens can be taken conveniently, inexpensively, and indefinitely for so long a time as menopausal symptoms persist?

Griffith<sup>6</sup> seems convinced that control of the artificial menopause is often an unsatisfactory experience and sometimes "it is a woeful failure." He believes, by way of explanation, that we as yet have little knowledge concerning the extent to which ovarian hormones enter into enzymatic reactions, and no reason to feel that the "main hormones" whose production many now regard as the sole function of the ovary really account for all the actions of the ovary in the body economy. Recent publications suggest that elaborations of the ovary contribute to both the nutrient and cardiovascular enzyme systems. Present-day substitutional therapy replaces only the estrogenic function of the ovary. When the total picture of ovarian function is better known, Griffith believes there will be less of the now prevalent practice of removing the ovaries when hysterectomy is indicated.

The last point in Emge's<sup>5</sup> outline refers to the most questionable of the statements offered as evidence of the harmlessness of removing ovaries. It has not been my experience that removal of the ovaries "does not involve the 'psyche.'" Rogers<sup>8</sup> has recently concluded that "the symptoms of menopause that are the most troublesome, and most frequently send patients to their physicians, are not related to diminished estrogens but usually to the psychological conflicts of middle age." With this I agree, though I certainly do



not believe Rogers intended to imply that woman could, with no greater difficulty, cope with the psychological conflicts of middle life after removal of her ovaries.

In the minds of all women, the loss of ovarian function is associated with old age. I am convinced that anything we can do to help a woman feel younger really helps her, and that whatever we may do that makes her feel older is not helpful. Psychologically, the worst thing we could do for her would be to make certain that a woman would feel old for a longer time. Are we sure we are not doing just that, when we remove her ovaries—incidentally or prophylactically?

We might briefly consider the premise that life today is not as easy for the modern woman as it might appear to be. A sizable proportion of grandmothers no longer keep a big old house prepared for "the children to come home." Many have moved into conveniently small, well-equipped apartments. Not a few enjoy every modern aid to housekeeping, with "everything on one floor," extension phones, and a pushbutton kitchen. So far as we can see, Mom never had it so good. All of this may be absolutely true most of the time, and yet Mom may become sensitive, frustrated, seemingly on edge, and ill at ease. We, her relatives and her physicians, are not of much help with the trite comment that she needs more to do.

To understand her we must consider the older woman's plight. Children and grandchildren scattered far, she is no longer the beloved Granny whose home meant a temptingly full cookie jar for the kids and pleasant memories for all. Today she is criticized if she stays home all the time, exhausted if she persists in a round of activities, frustrated at every turn if she tries to work for the good causes bidding for her attention. We hastily conclude that, for no good reason, she is worried. If we give her future a thought, however, it is apparent why anxiety clouds her thoughts.

Mothers, wives, and women independently employed, none escape the conviction that, in all probability, they will simply live too long. Fear of losing the economic independence they enjoy becomes an underlying source of tension. The suggestion that women are not biologically fitted for the long life we can now assure them is worthy of our serious thought. Perhaps the menopause, as modern women face it, is a biological accident. Perhaps women were not meant to live long past their menopause. We all know that fifty years ago their life expectancy was 48.7 years. Two generations ago, the psychological conflicts of what we now consider "middle age" were not a problem. Few of our grandmothers lived long enough to learn the meaning of geriatrics. In those good old days, however, many men outlived two wives. Today's woman must expect to live 72.4 years, and knows she is almost certain to outlive her husband by at least several years.

Shelton<sup>9</sup> believes that as women grow older anything that keeps them looking, feeling, and acting younger will be employed with or without the sanction of the medical profession. The drugs and psychotherapy advocated by so many may help to alleviate the hot flushes and the panic reactions incident to the menopause, but Shelton reminds us that they will not postpone the aging process. To at least some extent, he believes that estrogen will.

Considering the effects of estrogen withdrawal, it is difficult to believe that oophorectomy will not affect the psyche. Growing old presents problems that sooner or later nearly all women must face. To date there is little evidence to suggest that we help them in any way when we remove their normal ovaries, whether incidentally, routinely, or prophylactically.

At least three aspects of this discussion perhaps warrant additional comment. First, if we assume that ovarian function is important and desirable

after the menopause, should not all women who develop postmenopausal symptoms receive estrogens for the rest of their lives. For at least that proportion of women who eventually develop discomforts referable to atrophic changes, there are attractive arguments in favor of long-continued therapy. Investigators and physicians alike are beginning to ask about the atrophic changes in the genitourinary tract and skin, and about atherosclerosis and osteoporosis—are these not preventable lesions? Since endogenous sources of estrogen seem to protect many women against the development of all such disorders, one wonders—is prophylactic oophorectomy ever justified? Those who suggest that the ovaries should be removed whenever a hysterectomy seems indicated believe that: (1) to do so will forever remove the possibility that their patient's death might someday be due to ovarian malignancy, and (2) present-day substitutes for ovarian hormones are so effective that oophorectomy need make no change, physiologically or psychologically. If prophylactic oophorectomy is reasonable, for such reasons it is evident that we should not overlook the opportunities of preventing cancer of the breast by similarly prophylactic bilateral simple mastectomy. The chance that any woman's death may be due to carcinoma of the breast is at least twice as great as the probability of death due to ovarian malignancy. Moreover, many women seem to find that the breast substitutes now available to postoperative patients at least look like an improvement on nature.

Finally, it is important to remember that, even if universally practiced, so-called prophylactic oophorectomy would not reduce the over-all picture of ovarian malignancy to a significant extent. Not more than 15 per cent of women are likely to be subjected to pelvic laparotomy after their fortieth year. The removal of both ovaries in all women operated upon after 40 could therefore not be expected to reduce the over-all occurrence of ovarian malignancy by more than a corresponding 15 per cent of the total probability figure. In other words, removing both ovaries of the 150 women subjected to pelvic laparotomy after 40 among each 1,000, would simply reduce the eventual incidence of ovarian cancer from eight to seven cases among those 1,000 women. From the standpoint of the prevention of ovarian cancer, castrating the 150 women operated upon for benign uterine disease could be expected to accomplish nothing more than to assure that the death of one less woman per 1,000 would be due to a malignancy of the ovary.

In conclusion, is it not evident that the advisability of preserving the ovary may be questioned for some time to come? Before we advise women to have their ovaries removed, remember that only two generations ago no one knew that the ovary produced estrogens. Can we be sure, even today, that we know all that the ovary contributes to our patient's well-being?

Who can say that women do not need ovaries as they face a quarter of a century of "life after the menopause"? Let us remember that women have not been asking to have their ovaries removed either incidentally, routinely, or prophylactically. Most of our patients will outlive us. As they face the climacteric it is one thing to have tried to help them with advice and hormones, quite another to have removed their ovaries because at the time we thought it was a good idea. Eventually, we might well remember, they too will have learned more about ovarian function after the menopause.

#### References

1. Aeppli, H., and Rosenmund, H.: *Gynaecologia* 131: 404, 1951.
2. Allen, E.: *J. A. M. A.* 116: 405, 1941.

- 3, a. Bureau of Cancer Control: Levin, M. L., and Goldstein, H.: Presented at a Meeting of the Fourth International Cancer Research Congress, St. Louis, Sept. 2-7, 1947.
- b. Goldberg, Irving, Levin, M. L., Gerhardt, Paul R., Handy, V. H., and Cashman, R. E.: *J. Nat. Cancer Inst.* 17: 155, 1956.
4. Doyle, James: *J. A. M. A.* 148: 1105, 1952.
5. Emge, Ludwig A.: Discussion of Dowsett, J. W.: *West. J. Surg.* 63: 160, 1955.
6. Griffith, George C.: *Obst. & Gynec.* 7: 479, 1956.
7. Miller, Norman: *New York J. Med.* 42: 1851, 1942.
8. Rogers, Joseph: *New England J. Med.* 254: 697, 750, 1956.
9. Shelton, E. K.: *J. Am. Soc. Geriatrics* 7: 263, 1952.
10. Struthers, R. A.: *Brit. M. J.* 1: 1331, 1956.

### Discussion

DR. EMERSON K. BLEWETT, Austin, Texas.—In defense of prophylactic removal of ovaries after age 45, I might quote two series of case reports.

The Philadelphia Committee for the Study of Pelvic Cancer reported on nearly 300 cases of ovarian carcinoma in which 9 patients had had a previous hysterectomy without removal of the ovaries, above age 45.

Counseller, reporting on 1,500 cases of ovarian cancer seen at the Mayo Clinic from 1930 to about 1952, reported 65 cases of carcinoma of the ovary which had developed after a previous hysterectomy.

These case reports certainly emphasized that these patients would have been alive had prophylactic removal of the ovaries been performed.

DR. ROGER S. SIDDALL, Detroit, Mich.—I wanted to point out, first of all, that this matter does not concern carcinoma of the ovary only. The point was brought out by Dr. Randall. There are other tumors, cystomas, fibromas, and such tumors, which may occur about four to five times as frequently as carcinoma.

In other words, instead of 1 per cent of these women having carcinoma, 4 or 5 per cent may have tumors if the ovaries are left in. It should be remembered that all of these neoplasms can kill, as carcinoma can kill, although not in the same proportion, it is true.

I was not going to discuss that, particularly, but I did want to point out that there is another solution to the problem, or at least a partial solution, and that is the removal of one ovary. I know that is rather widely practiced. There is the question of whether or not the removal of one ovary will reduce the chances of these tumors 50 per cent. The only opinion that I can find is that of Gardner of Chicago, who says that many doubt that the removal of one ovary will reduce the number of ovarian tumors 50 per cent.

Starting from that point, I have for a number of years made the observation that ovarian tumors occur more on one side than the other—on the left side. Whether or not that is true in the experience of others I do not know, but recently Levine and I collected a group of 500 cases of neoplasms of the ovary, including carcinoma,\* and our findings were that, of the tumors we studied, a considerably greater percentage occurred in the left ovary, with the exception of fibromatous tumors, in which there was only a slight difference.

That being the case, we wondered whether it was not possible, perhaps, to at least approach a 50 per cent reduction of tumors in later life. So far as we can tell from the literature and studies, the remaining ovary will satisfactorily take over the functions of both ovaries.

DR. C. GORDON JOHNSON, New Orleans, La.—First of all, Dr. Randall, what is your opinion regarding the removal of ovaries in breast cancer?

And you did mention something about estrogen for the menopause, but did not go into any detail. I wonder if you would give us your opinion on the continued use of estrogens after the menopause? By "continued," I mean over a matter of years. At

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times we will see a patient—and I'm sure you do, as well—who has been treated by internists for several years with the continued use of estrogens, either given by injection or by the oral route.

DR. GILBERT F. DOUGLAS, Birmingham, Ala.—Those of us who have lived and practiced gynecology as long as a quarter of a century—and I judge that a great percentage of this audience has lived that period of time—have seen and heard many discussions pro and con as to the removal or use of conservative measures in the matter of the ovaries.

In my earlier years, I was trained with one man, an outstanding man in the nation, who did oophorectomy routinely in practically every hysterectomy he did on a patient who was above 30 years of age. I am sure that if he were living now his concept would have been changed considerably.

Well, that put a great question in the public's mind, as to whether a man as brilliant as he was doing the best thing for our profession on the assumption that by removing these ovaries, he was preventing cancer formation later.

Personally, I feel that whenever an ovary or part of an ovary can be conserved, we are doing something for the individual. The psychiatric phases that develop after the removal of ovaries are sometimes rather astounding.

To mention a case to illustrate the point, within the last two months I had a patient come from out of town who had been a patient of mine for several years. We had been watching her on account of her bleeding. She was then 57 years of age, and would have bouts of bleeding at intervals, maybe two months or three months apart; generally speaking, it was about in that range.

On checking her over, we found a neoplasm or growth which proved later to be benign. There were adenomyosis and endometriosis.

When she got to the point of being operated on, she became so disturbed that she was ready to leave the hospital the night before the operation was to be done. The spot she had me on was this: "Are you going to remove the ovaries? Regardless of what you do, leave the ovaries in." She had previously received radium, which seemed to have upset her mentally. She agreed to stay on for the operation and had a smooth recovery, but she had a perfect phobia that, if the ovaries were removed, the next step would be to have her committed to an institution because of the nervousness which she would undergo.

I am a firm believer in Bonney's concept of doing cystectomies in the ovaries, and removing a portion of the ovary. I believe the patients are much better off, and it pays off from a sterility standpoint, too, because in the occasional case where you have removed rather large cysts from both ovaries, and you have done a cystectomy, the patient is able to have a baby when she was not able to have one before.

DR. CARROLL J. FAIRO, Cincinnati, Ohio.—I have been in gynecology now for the 25 years that the doctor spoke of, and it seems like we get into cycles. A few years ago we were so excited that we were taking out all the ovaries. Then someone comes along and says, "Take one out." I think we can draw a happy medium here. I believe as we leave here, most of us are going home with the idea of leaving them all in.

It is amazing, how many patients are operated on and never know what they are operated on for. I think we should explain to these patients what will happen and what will not happen, because some patients have a cancer phobia, so that they are worse off than ever if they have an ovary in. I think there are a few women who would rather have them out.

DR. JOSEPH E. KOPCHA, Gary, Ind.—The late Dr. Bertha Van Husen will go down in history, I think, for this remark: "A testicle is not bad enough to remove, and an ovary is not good enough to save."

I have been all over the world, and I have seen noted surgeons carry great big trusses for their hernias; they will walk into the operating room and operate on everybody else's hernias, but they will save their own.



I have seen the same professors do the same thing with gastric ulcers, with the removal of stomachs for ulcers or carcinomas, but they will protect their very own ulcers with little tablets of Gelucil, and can carry them on through the rest of their lives. When it comes to somebody else's testicles or ovaries, they take them out. My feeling on that is, let us be as gracious with someone else's organs as we would with our own.

To sum up the whole thing, I think Dr. Schindler, in his book *How to Live 365 Days a Year*, brings out that very thing—if you want to live with your patients, treat them as you would your own wife.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—I could not help but think that there must have been many times when Joe Kopcha was All-American that he wished he was carrying those in the location of the ovaries.

There are two questions that I do not believe have been clarified, or at least they have not been for me.

One is this present-day problem of having the surgical brethren in the hospital refer patients to us for oophorectomy following radical mastectomy for carcinoma.

There seem to be two schools of thought, one for performing immediate oophorectomy and then using the androgens, eventually going to adrenalectomy and now, finally, to hypophysectomy; the other group is opposed to immediate oophorectomy, preserving that for the time when there is an osteogenic recurrence. I would like to know what Dr. Randall thinks about those ovaries.

In the other situation that has not been mentioned, what are we going to do with the ovary in endometriosis? In our so-called conservative approach, in attempting to preserve the function of the individual, are we going to leave the ovary behind? In the more advanced case, are we going to sacrifice the uterus and leave the ovary, or shall we remove the ovary and the uterus?

DR. RANDALL (Closing).—Of course, this problem is one that is difficult to divorce completely from one's personal bias. I am sure that in many instances our individual conclusions about this problem date back to the day when a patient on whom we had performed a hysterectomy, preserving the ovary, returned with an ovarian carcinoma. This is such a deplorable experience that it is apt to make the problem assume an importance in our minds out of all proportion to the statistical chance that it will occur.

In response to some of the questions, I am familiar with the experience of the Philadelphia group, and appreciate the fact that in those 300 cases of ovarian carcinoma, 9 women had had a previous hysterectomy. I think that figures out about 1 in 33 women developing a carcinoma of the ovary who had previously had a hysterectomy. Considering the infrequency of ovarian carcinoma, it almost seems that you would have to do 33 times as many hysterectomies as there are ovarian cancers to affect the problem.

I do not think we should quote Dr. Counseller's series as evidence that leaving in ovaries provides much of a risk for the subsequent development of ovarian cancer, because Dr. Counseller admitted readily at the time he gave the report that he did not know how many cases of hysterectomy these 65 cases of ovarian carcinoma followed. He knew that 65 women had come into the clinic with ovarian malignancy who had previously had a hysterectomy, but he had no idea how many hysterectomies that group of 65 represented.

Now, as to the question of how much pathology other than carcinoma of the ovary may develop in the ovaries that we preserve, I have not any definite figures after the age of 40; however, I do have a very definite impression. If you study the series of ovarian neoplasms that have been reported in the literature, I think you would be impressed by the fact that the vast majority of benign ovarian neoplasms develop before the age of 45. If your patient needing a hysterectomy is 45 years of age, she has passed up most of her chances of developing a benign neoplasm of the ovaries.

We are quite sure that among women more than 50 years of age, only 14 in 1,000 will ever develop any neoplasm in the ovary, and that 8 of those will be malignant and 6 will be benign, so I do not think we are subjecting them much to the probability of another laparotomy.

Except for the adenocystomas, we do not recognize any women who are particularly predisposed to ovarian carcinoma, and so we have to treat this problem on a somewhat statistical basis.

In regard to removal of the ovary in the management of carcinoma of the breast—I think Dr. Schmitz practically answered that in asking the question. It has now become evident that the ovary is only one source of estrogen, and that if it is logical to do so-called prophylactic oophorectomy on women because they have carcinoma of the breast, our chances of removing all estrogen from that woman's body are not too good. Struthers' smears indicated that only 20 per cent of women had a complete lack of estrogen, and yet the incidence of estrogen was only 14 per cent less among women who had their ovaries removed, so, as Dr. Schmitz implied, if we are going to castrate women in order to help them better handle their carcinoma of the breast, we need to do more than remove their ovaries. The adrenals and other tissues are also sources of estrogen.

I think we are all convinced that women who have metastatic carcinoma of the breast, particularly metastatic in bone, will achieve a good deal of symptomatic improvement if they are castrated, particularly the younger women, but I also believe that the routine castration of normal younger, premenopausal women has not been shown to make any great over-all change in their life expectancy if they have carcinoma of the breast.

In answer to Dr. Johnson's question about the use of estrogens after the menopause, I feel very strongly that the first thing to determine is whether the woman needs estrogen, because many women continue taking them long after they need to. Prolonged estrogen therapy should be interrupted occasionally, to see if they do equally well from a symptomatic standpoint without it.

As to the question, why not take out one ovary, I admit that one defeats me. I have no answer to it. I know many individuals whose opinion I respect who simply sidetrack this whole controversy by saying, "I cut out one ovary and cut the chance of ovarian malignancy down 50 per cent." Whether they actually do or not is still not known, but at least they are preserving a good deal of ovarian function.

Regarding the question of what to do with the ovary in endometriosis, I'm sure that the management of endometriosis has to be a highly individualized problem. I know of no other answer to give to that question. Sometimes the only way we can control endometriosis is by castration. I must admit that sometimes it seems justified.

## **SERIAL OXYGEN SATURATION STUDIES OF NEWBORN INFANTS FOLLOWING OBSTETRICAL COMPLICATIONS, DIFFICULT DELIVERIES, AND CESAREAN SECTION\*†**

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**T**HIS investigation was originally prompted from observations that the oxygen saturation levels of newborn infants following maternal, fetal, and obstetrical complications were diminished as compared to those of infants born in normal deliveries. Further studies seemed indicated since these findings substantiated a clinical opinion that infants born after maternal or fetal complications, excessive analgesia or general anesthesia, and abnormal presentations or difficult delivery were the infants that required greater resuscitation and newborn care. We have further been interested in the oxygen saturation levels of infants born by cesarean section.

Previous publications<sup>1, 2</sup> from this Department have reported serial chemical studies done on capillary blood oxygen saturation levels of premature and full-term infants following various types of anesthesia. Later publications<sup>3</sup> reported the effects of Demerol and trichloroethylene on the arterial saturation levels in the newborn as determined by the use of the photoelectric infant oximeter earpiece. The currently reported investigation was designed to study the effects of obstetrical disease on oxygenation of the newborn.

### **Materials and Methods**

A double-scale, absolute-reading, alternating-current oximeter with an infant-sized earpiece was used in all determinations in the current study. The instrument† is devised for the photoelectric determination of absolute values of arterial oxygen saturation in the intact lobe of the human ear. Wood and Geraci<sup>4</sup> have described the physical principles of the unit. Our results were not checked chemically, but previous work by other investigators<sup>5</sup> has shown the standard deviation of the difference between the photoelectric and Van Slyke determinations of the arterial blood oxygen saturation to be 2.9 per cent. The photoelectric oximeter was ideal for this study because it is possible to make continuous direct readings of the arterial oxygen saturation for an indefinite period. A total of 66 full-term infants were studied by this method.

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‡The machine is manufactured by Waters-Conley Company, Rochester, Minn.

All the infants survived and were discharged from the hospital as normal newborns. Serial readings were made on each infant with the photoelectric oximeter from birth each two minutes to one-half hour of life. The infants studied and the obstetrical particulars are listed in Table I.

TABLE I

OBSTETRICAL CONDITION	ANESTHESIA	DELIVERY	CASES	RESULTS
a. Normal	Pudendal block without analgesia	Spontaneous vaginal	13	Fig. 1
b. Moderate analgesia	Pudendal block	Vaginal	9	Fig. 1
c. Normal	Saddle block	Vaginal	10	Fig. 2
d. Obstetrical complications	Saddle or caudal block	Vaginal	14	Fig. 2
e. Severe complications	Inhalation	Vaginal	5	Fig. 3
f. Cesarean section	Spinal	Cesarean section	15	Fig. 4
Total			66	

Observations were also made on the effects of therapeutic oxygen administration and resuscitation on the oxygen saturation levels of the newborn.

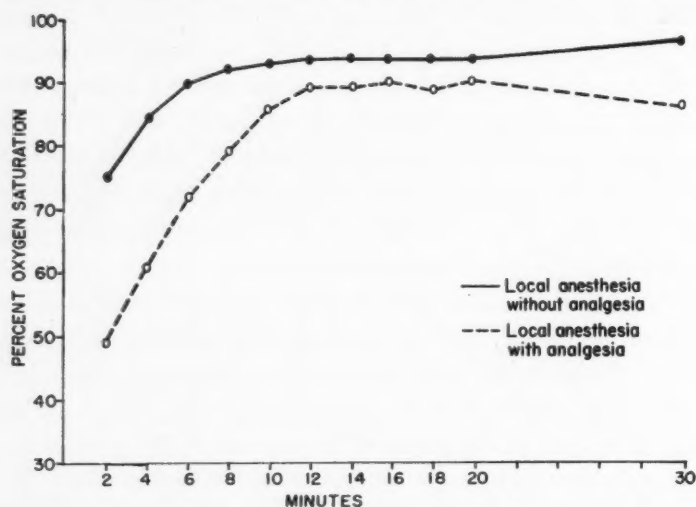


Fig. 1.—Curve of neonatal oxygenation during first 30 minutes of life, comparing normal physiological delivery to vaginal delivery with maternal analgesia given one hour before delivery.

### Results

*A. Normal or Control Series, Uncomplicated Vaginal Delivery With Pudendal Block Anesthesia (13 Infants).*—Inspection of Fig. 1 shows that the thirteen infants in the normal or control series had an average arterial oxygen saturation level of 75 per cent two minutes after birth. The extremes in oxygen saturation at two minutes were 63 per cent and 96 per cent. The average level at six minutes was 90 per cent oxygen saturation. The average level at thirty minutes was 95 per cent. All the mothers had uncomplicated prenatal and intrapartum courses and did not receive any analgesia within one hour of delivery. The duration of labor varied between three and eight hours. All deliveries were spontaneous from the occiput anterior position and conducted under pudendal block anesthesia. There were 12 multiparas and one primipara in this series. The results in this group are almost identical with those reported previously.<sup>3</sup>



*B. Effect of Moderate Analgesia on Oxygen Saturation of the Newborn (9 Infants).*—The average saturation levels of infants born after recent maternal analgesia and pudendal block anesthesia are also shown in Fig. 1. The infants were mildly depressed at birth, and the average saturation level at two minutes was 49 per cent as compared to 75 per cent in the control group. The saturation level at six minutes was 72 per cent as compared to 90 per cent in the normal series. At the end of thirty minutes the average level was 86 per cent in the relatively complicated group as compared to 95 in the control series. This part of the study demonstrates the effect of analgesia given shortly before delivery on full-term infants. Six of the mothers received a combination of intravenous Demerol (50 mg.) and intramuscular Demerol (50 mg.) within one hour of delivery, and 2 mothers received morphine sulfate within ninety minutes of delivery. Three infants were delivered by outlet forceps, 5 spontaneously, and one by breech extraction. Eight labors lasted four hours or less, and the other one eight hours. The average curve of oxygen saturation in the first twenty minutes after delivery in the analgesia group was statistically significant when compared to data from infants whose mothers received no analgesia one hour or less before delivery.\*

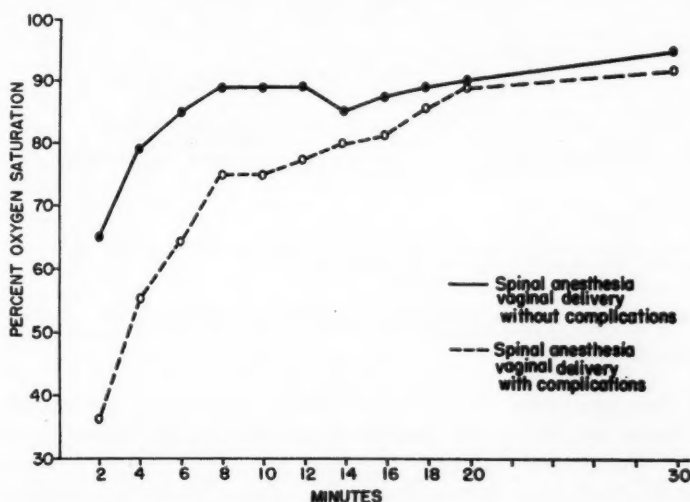


Fig. 2.—Curve of neonatal oxygenation during first 30 minutes of life, comparing spinal anesthesia without complications to spinal anesthesia in the presence of recent analgesia or complications of pregnancy and labor.

*C. Effect of Saddle Block Anesthesia (10 Normal Parturients).*—Ten mothers with full-term, uncomplicated pregnancies and normal intrapartum courses were given heavy solution of Nupercaine (2.0 to 2.5 mg.) intrathecal anesthesia. The infant arterial saturation levels are shown in Fig. 2. The average arterial oxygen saturation level at two minutes in this series was 65 per cent, the average level at six minutes was 85 per cent, and at thirty minutes was 93 per cent. The extremes of the level at two minutes were 30 and 92 per cent. No analgesia was given within one hour of delivery. The average duration of saddle block anesthesia before delivery was thirty-four minutes. There were 4 primigravidas and 6 multigravidas. There were 6 outlet forceps deliveries, and 4 spontaneous deliveries. All presentations were occiput anterior. The duration of labor varied from four to twelve hours.

\*According to the "t" test, up to twenty minutes these data are statistically significant. Calculations done by Dr. Jack Dodge and Mr. Edmund Weiss.

*D. Oxygen Levels in Newborn Infants Born After Conduction Anesthesia in the Presence of Obstetric Complications (14 Infants, Fig. 2).*—The lowest arterial oxygen saturation level at two minutes was 18 per cent, which occurred in one 3,210 gram infant whose mother had severe pre-eclampsia, uterine inertia, intravenous Pitocin stimulation, continuous caudal anesthesia (for four hours), a fifty-three hour labor, and delivery by low forceps. The highest saturation level at two minutes for the group was 64 per cent. The average saturation level at two minutes was 38 per cent and the average at six minutes was 64 per cent. An 80 per cent average saturation level was not attained until fourteen to sixteen minutes following delivery. The average saturation level at thirty minutes was 91 per cent.

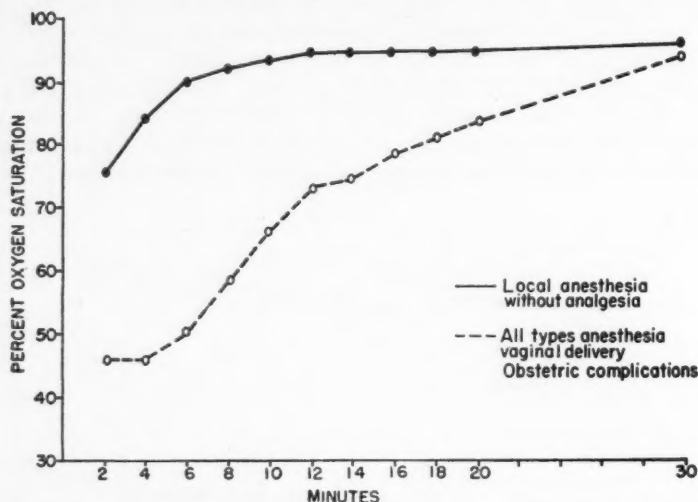


Fig. 3.—Curve of neonatal oxygenation during first 30 minutes of life, comparing normal physiological delivery to deliveries performed in the presence of severe complications of pregnancy and labor.

This group demonstrates the effect of major operative obstetrics and maternal complications on the early neonatal period of the infant. All infants were full term. There were 5 primiparas and 9 multiparas. There were 3 mothers with mild to severe pre-eclampsia. There were 3 occiput posterior presentations and one face presentation. Two mothers of the entire group received analgesia within one hour of delivery. Eight of the 14 patients in this series were delivered with low forceps. The average duration of spinal anesthesia before delivery was forty minutes. These differences in oxygen values when compared to the values of patients who had spinal anesthesia without complications were statistically significant.\*

*E. Patients With Severe Obstetrical Complications Delivered With a Small Amount of Cyclopropane General Anesthesia (5 Patients, Fig. 3).*—Included in this group are severe abruptio placentae, prolapsed cord in a breech presentation with full dilatation, prolonged labor of fifty-one hours where intravenous Pitocin was used, and a difficult breech delivery in a primipara.

The average saturation level two minutes after birth was 46 per cent, 49 per cent at six minutes, 80 per cent at eighteen minutes, and 93 per cent at thirty minutes. Despite energetic resuscitation in 4 of these infants, the delay in the rise in oxygen saturation is noteworthy. The longest duration of cyclopropane before delivery was ten minutes and in most cases it was less than five

\*According to the "t" test.

minutes. The comparison of the oxygen values attained by this group during the first one-half hour of life as between normal physiological delivery and uncomplicated delivery is highly significant.\*

*F. Spinal Anesthesia With Cesarean Section (15 Infants, Fig. 4).*—Fifteen mothers were delivered by cesarean section under spinal anesthesia. There were 12 repeat cesarean sections, 2 for placenta previa, and one for maternal diabetes. The average oxygen saturation level at two minutes was 65 per cent. The extremes were 40 to 79 per cent. The average saturation level at six minutes was 74 per cent and the average at thirty minutes was 94 per cent (Fig. 4). As may be seen from Fig. 4, there is a reduced level of oxygen saturation when infants are born by cesarean section, but the effect when it is a single factor is probably not clinically significant. Spinal anesthesia and cesarean section combine to give lowered oxygen saturation values, and the difference between the levels in these infants and those born normally is statistically significant only for the first fourteen minutes.\*

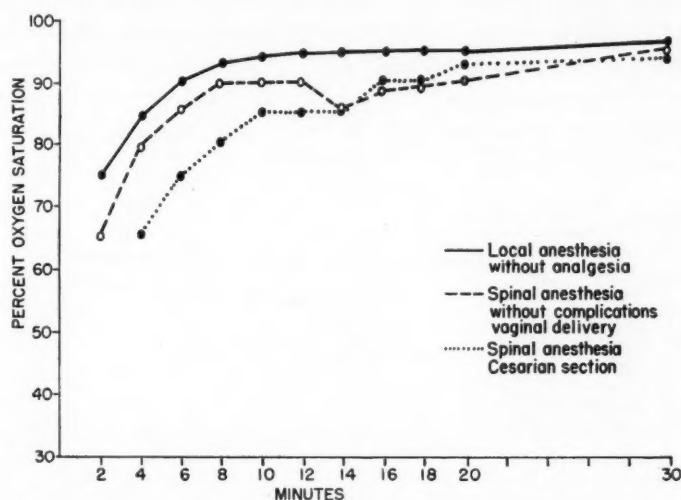


Fig. 4.—Curve of neonatal oxygenation during first 30 minutes of life, comparing physiological delivery to delivery under spinal anesthesia; and finally a curve showing the combined effect of spinal anesthesia and cesarean delivery on neonatal oxygen levels.

It is apparent that the lag in oxygenation following cesarean section under spinal anesthesia is a finding that is secondary to the combined action of spinal anesthesia and cesarean section.

#### Comment

The chemistry of infant respiration both in the uterus and outside of the uterus is an extremely complex problem. The study of the newborn child's rise in blood oxygen levels during the early minutes of life is but one of the many aspects of respiratory activity that is measurable. Our measurements are not precise quantitative measurements but rather trace a trend in the physiological adjustment of the newborn during the first half hour of life. The normal full-term infant follows a rather characteristic and quick adjustment to extrauterine life if unimpeded by disease, drug, or trauma. Even

\*According to the "t" test.

safe amounts of maternal analgesia can be demonstrated to reduce normal physiological oxygenation in a measurable fashion. Analgesia, if a single depressing factor for a full-term infant, is not in itself clinically significant so far as the newborn is concerned. Only when the effect of analgesia is added to other factors depressing fetal respiration is moderate analgesia dangerous. We have previously shown<sup>1, 2</sup> that prematurity and maternal general anesthesia each render some degree of respiratory depression to the newborn as indicated by serial blood oxygen studies.

It is well known that perinatal mortality is higher in infants born from mothers who exhibit complications of pregnancy. It is quite infrequent that pathological studies of infants that die during labor or in the early neonatal period demonstrate gross brain hemorrhage or tentorial lacerations. The majority of intrapartum deaths and neonatal deaths are, after thorough gross and microscopic study, credited to anoxia, hypoxia, atelectasis, or hyaline membrane. All of these may be grouped as deaths from respiratory failure. Perhaps analgesia, anesthesia, prematurity, and maternal complications when added together in a particular patient cause intrapartum and neonatal hypoxia and death. This may even be true in full-term infants, depending on the severity of depressing factors.

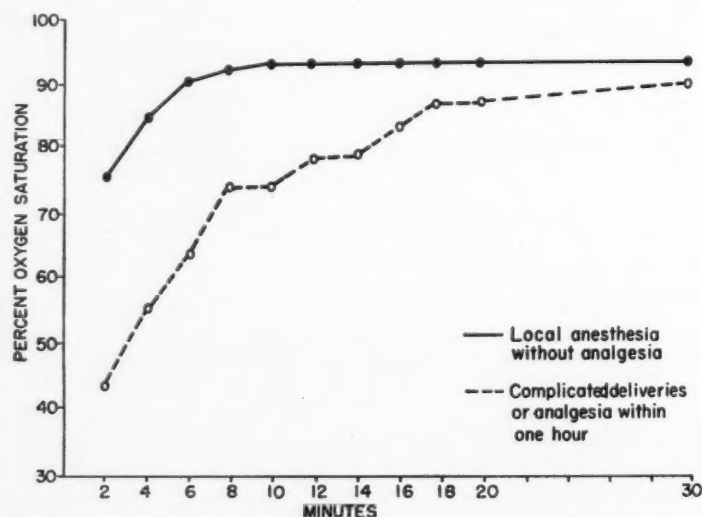


Fig. 5.—Curve of neonatal oxygenation during first 30 minutes of life, comparing physiological delivery to deliveries performed after recent analgesia and in the presence of complications of pregnancy and labor (sections *b*, *d*, and *e* of Table I).

The fetus in the nonlaboring uterus near term thrives in an atmosphere which provides him with blood 50 to 60 per cent oxygen saturated. Walker<sup>6, 7</sup> has reported that toxemia and postmaturity reduce the intrauterine oxygenation of umbilical vein blood to hypoxic levels even before labor ensues. The maintenance of proper levels of blood oxygenation to the fetus in utero is dependent on adequate maternal blood pressure and an adequate oxygen-carrying capacity of fetal blood. Hypertonus of the uterus such as is associated with toxemia of pregnancy and with the injudicious use of pituitary extract during the first stage of labor will interfere with proper uteroplacental



circulation and will reduce fetal oxygen supply. Should considerable analgesia and anesthesia be added to depress an already hypoxic child, such drugs may be the factor which makes the establishment of normal extrauterine respiration difficult or impossible.

Our study has demonstrated that factors superimposed during labor other than maternal analgesia and anesthesia may have a profound effect on the oxygenation of the fetus and the newborn. The mechanisms of these hypoxic changes in the fetus vary greatly. Placental separation and prolapsed cord are not difficult to understand as major contributors to fetal hypoxia and a delay of oxygenation of the infant during the early neonatal period. Prolonged labor, on the other hand, has not been generally recognized as being an important factor in a progressive depression of fetal oxygenation. As shown by Caldeyro,<sup>8</sup> prolonged labor, intravenous Pitocin, and abruptio placentae are associated with increased and pathological degrees of uterine hypertonus. This, when prolonged, has a progressively adverse effect on uteroplacental circulation and presumably therefore on fetal oxygen supplies.

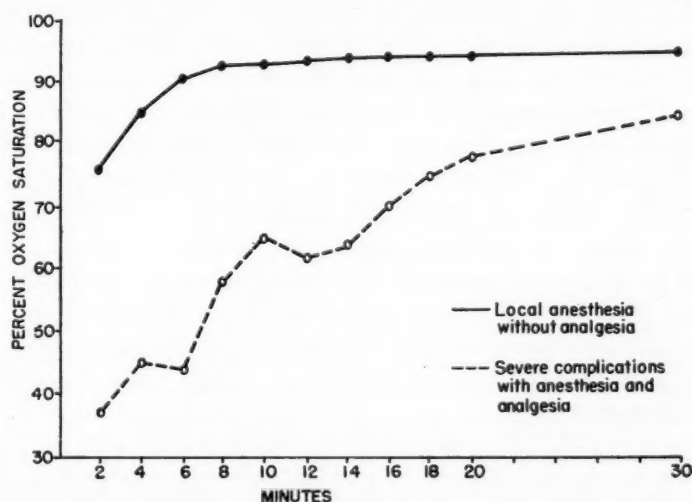


Fig. 6.—The effect on neonatal oxygenation of the severest complications of labor.

In order to emphasize the importance of complicated or pathological obstetrics on the newborn's oxygenation, we have prepared a graph, Fig. 5, to summarize the effects of adverse obstetrical pathology on the oxygenation of the infant's blood during the first one-half hour of life. This graph is an aggregate of results obtained when the mothers had received recent analgesic sedation or had complications of pregnancy or delivery (see sections *b*, *d*, and *e* of Table I). This is further emphasized by a graph, Fig. 6, which shows the effect of the severest obstetrical complications on the neonatal oxygenation of 7 infants. These complications were pre-eclampsia, face presentation, abruptio placentae, breech and prolapsed cord, morphine analgesia, and prolonged labor with Pitocin induction.

Bruns<sup>9</sup> has recently demonstrated that there is a significant reduction of uterine circulation time in pregnant patients with pre-eclampsia, premature labor, premature rupture of the membranes, and abruptio placentae. This

work was done utilizing the disappearance rate of radioactive sodium from the uterine musculature. The demonstration of reduced uterine circulation in such patients is significant in relation to the respiratory reserve and oxygen supply that the uterus affords the fetus when these maternal complications are present. The reduced circulation time may be related to Walker's<sup>6</sup> findings that have disclosed low umbilical vein levels of oxygen when toxemia is present.

Montgomery<sup>10</sup> has studied serial oxygen levels in the infant born after cesarean section when spinal anesthesia is used. His findings correspond with ours in that there is a statistically significant depression in levels of blood oxygen at birth and also a significant lag in the progressive oxygenation of the baby born by cesarean section as compared to the normal infants born by uncomplicated vaginal delivery. While this depression and lag are present in cesarean section infants, we do not believe them to constitute a significant single factor in fetal prognosis. We therefore continue to use low-dose spinal anesthesia for elective cesarean section if there are no fetal or maternal contraindications. None of our 15 cesarean section operations were complicated by a hypotensive reaction to the spinal anesthesia. We do not know the reason for the peculiar findings in the blood oxygen levels during the first hours of life in cesarean newborns. The clinical significance of this finding relates to the use of spinal anesthesia when the fetus is already compromised by one of the complications of pregnancy. We feel that in any given situation the obstetrician must consider all the potentially adverse elements that may affect fetal oxygenation. Most important are maternal complications and difficult delivery as they affect the uterus. Secondary factors which may be added in the case of an already hypoxic child are the respiratory depressing effects of analgesia, general anesthesia, or cesarean section. Whether the depression of normal physiology that analgesia, anesthesia, or spinal anesthesia induces is significant or not depends on what other things have or have not compromised the oxygen supply.

In the course of these experiments we have found that oxygen administered to the hypoxic child always benefits the child if his respiratory exchange apparatus can be made to function. One other interesting finding has been that nasopharyngeal suction with a catheter attached to a negative pressure machine often promotes transitory fetal hypoxia. If serial oxygen saturation determinations are made on a child while it is adjusting from 50 to 95 per cent oxygen saturation during the first one-half hour of life, nasopharyngeal suction causes a precipitous temporary drop in fetal oxygen levels. It has also been found during this study that clamping of the umbilical cord while it still pulsates will cause a sudden drop in blood oxygen values. Should the operator clamp the cord only after pulsations have ceased, the fetal oxygen levels are unaffected.

### Conclusions

1. Demerol analgesia produces a statistically significant depression in neonatal blood oxygenation but not a clinically significant depression if the usual doses are used and if there are no other important respiratory depressing factors present.

2. Complications of pregnancy such as placental disease, prolonged labor, toxemia of pregnancy and its management, and major operative procedures cause a profound depression of fetal respiratory activity, both at birth and during the early neonatal period.

3. Cesarean section under spinal anesthesia is accompanied by a statistically significant depression of blood oxygenation in the infant both at birth and during the early neonatal period. This, however, is not significant clinically unless compounded with other more serious handicaps to fetal respiratory physiology.

4. The reduced oxygenation of the newborn that is evident following cesarean delivery under spinal anesthesia appears to be a combined effect of the spinal anesthesia and the cesarean operation.

### References

1. Taylor, E. S., Govan, C. D., and Scott, W. C.: *AM. J. OBST. & GYNEC.* 61: 840, 1951.
2. Taylor, E. S., Scott, W. C., and Govan, C. D.: *AM. J. OBST. & GYNEC.* 62: 764, 1951.
3. Taylor, E. S., von Fumetti, H. H., Essig, L. L., Goodman, S. N., and Walker, L. C.: *AM. J. OBST. & GYNEC.* 69: 348, 1955.
4. Wood, E. H., and Geraci, J. E.: *J. Lab. & Clin. Med.* 34: 387, 1949.
5. Crehan, E. L., Kennedy, R. L. J., and Wood, E. H.: *Proc. Staff Meet., Mayo Clin.* 25: 392, 1950.
6. Walker, J., and Turnbull, E. P. N.: *Lancet* 2: 312, 1953.
7. Walker, J.: *J. Obst. & Gynaec. Brit. Emp.* 61: 162, 1954.
8. Caldeyro, R.: *Triangle* 2: 41, 1955.
9. Bruns, P. D., Taylor, E. S., Anker, R. M., and Droese, V. E.: *AM. J. OBST. & GYNEC.* 73: 579, 1957.
10. Montgomery, T. L., Brandfass, R. T., and First, H. E.: *AM. J. OBST. & GYNEC.* 71: 1, 1956.

### Discussion

DR. JOHN C. ULLERY, Columbus, Ohio.—All of us have been aware of the higher perinatal mortality in infants born of mothers who show various complications of pregnancy, such as toxemia, abruptio placentae, placenta previa, and perhaps of mothers of advanced age, and in cases of postmaturity. Their studies substantiate this fact and add importance to the choice of analgesia or anesthesia as an added factor in the production of anoxia. Although they do not state in a one, two order, the various types of anoxia that may be present in utero and after birth, the implications are clear that one or more types may be involved.

An accepted classification of the different types of anoxia with examples may show the factors involved and serve to increase our awareness of the pathology that is present in utero or at birth.

#### TYPES OF ANOXIA

1. *Stagnant Anoxia.*—In this the blood flow is reduced or suppressed, resulting in a decrease or lack of oxygen supply to the nerve cells. Examples of this type in relation to the fetus would be abruptio placentae, toxemia with degeneration of the placenta, and prolapse or compression of the umbilical cord.

2. *Anemic Anoxia.*—In this type less oxygen is available in the blood stream of the fetus because of the smaller amount of hemoglobin present, so that only a small amount of oxygen can reach the nerve tissue of the brain. Vasa previa, cerebral hemorrhage, congenital heart lesions are examples in this group that would produce the anoxia.

3. *Anoxic Anoxia.*—This occurs where a smaller amount of oxygen will be absorbed in the blood, resulting in a lowered oxygen supply to the brain. Anesthetics, such as nitrous oxide, cyclopropane, and others in which the oxygen supply is lowered may be the responsible factor producing this anoxia.

4. *Histiotoxic Anoxia*.—In this the nerve cell membrane is damaged so that oxygen cannot be absorbed, even though it is present in adequate amount. Tentorial tears, traumatic lacerations of the brain, or developmental defects of the fetal brain are such examples.

This classification is shown to emphasize the many factors that can predispose to anoxia in the fetus. It serves to emphasize a cardinal fact that is presented here so well in Drs. Shields and Taylor's paper, namely, that when a potential lesion causing anoxia may be present, such as toxemia, or trauma, and a general anesthetic is superimposed, the oxygen saturation of the fetus is markedly affected, the anoxia is increased.

We thoroughly agree with the findings and value of the use of regional or local analgesics for vaginal or abdominal deliveries endorsed by the authors. An example of the low fetal mortality, low anoxia rate can be seen from a previous report by Lull and me at the Philadelphia Lying-In Hospital in 1948. One thousand cesarean sections were performed under continuous spinal analgesia, with an uncorrected fetal mortality of 4.7 per cent. Nine hundred and eighty-six babies were born alive in this series and only one baby required active and prolonged resuscitation.

DR. HERMAN I. KANTOR, Dallas, Texas.—I wish to ask one question. Did Dr. Shields do any prolonged studies on oxygen saturation—that is, studies which ran over a period of three or four hours, perhaps—to show a difference in the various groups which he presented?

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—I think we are all becoming oxygen conscious, in view of the guest speaker's paper yesterday, and this paper this morning. However, I think we should keep in mind that oxygen can be a poison. We should remember that all of us have some blind babies because we or the pediatrician, or both of us, thought that if a little oxygen was good, more was even better.

I think the Denver group has done an excellent job, along with the groups in Detroit and in Philadelphia, in showing that almost anything you do to the mother in the way of anesthesia or analgesic drugs does have a measurable effect on the baby.

Keep in mind that there are two types of circulation by which the baby gets its oxygen. We have been studying intrauterine circulation, and have learned that it is dependent on the maternal pulse, the maternal blood pressure, and other factors which we have been trying to measure over some fifteen years. We reported in 1941 a method for delivering the umbilical cord at the time of cesarean section, obtaining a control specimen and then giving the patient a spinal anesthetic, hypotensive drugs, cyclopropane, etc. All of these have a very definite effect on the oxygen saturation in the mother's blood, and, of course, it follows that if it decreases, the baby's oxygenation will also diminish.

In addition, during labor the contraction of the uterus acts as a pump and there is a very definite difference as to what you find in the oxygenation of the maternal blood and the umbilical cord at cesarean section under local anesthesia, compared to what you get at vaginal delivery, which is terminal.

Cyclopropane will drop the maternal oxygen saturation to about 94 per cent. Spinal anesthesia, without any demonstrable effect on blood pressure, will drop the oxygenation in the maternal and fetal blood appreciably, and if there is a drop in the maternal blood pressure, this decrease becomes greater.

I appreciate the dangers of cesarean section, but I cannot conceive of a baby born under similar conditions of anesthesia, namely, local, both by vaginal and cesarean section, with oxygen saturation differences lasting for 30 or more minutes.

I do not believe that the heel puncture in the baby represents true arterial saturation. We have tried the oximeter, and although Dr. Shields mentioned that there is an error of a little less than 10 per cent, I think it depends entirely upon what stage of oxygen saturation you are measuring.

I suspect that there is still some unknown factor concerned in these differences, but that does not detract from the conclusions in this report and those of the other two groups, that whatever drug you give to the mother does have a measurable effect on the baby.



DR. DAVID N. DANFORTH, Evanston, Ill.—First, I wish to ask whether Dr. Shields estimated the effect of anesthesia in uncomplicated vaginal deliveries on the oxygen saturation of the baby.

Second, I wish to know, specifically, what he considers to be the error of this method, and also how, in the light of that, he would interpret the significance of the differences that he has shown.

DR. CLYDE L. RANDALL, Buffalo, N. Y.—The thing that all of us would obviously like to know is how significant—in terms of the eventual welfare of this child, the eventual integrity of its nervous system—and how reliable are these oxygen saturation studies?

At the University of Buffalo, some seven years ago, a long-range study was set up in which oxygen saturation at birth and during the first hour of life was studied by an oximeter setup quite similar to the one Dr. Shields has employed. Those babies were subjected to quite thorough study during the first week of life, and they have been returned to the hospital, with the cooperation of the parents, for follow-up study. Some 400 infants have now been studied for five years or longer.

I think we must admit that we are going to have to be conservative in our interpretation of oxygen saturation measured at birth, from the standpoint that relatively small variations are not particularly significant. However, if we consider only those babies who show a significantly low oxygensaturation at birth, and are slow to gain 90 per cent, comparing those with the ones that relatively quickly gain a 90 per cent saturation, we find that there is a significantly increased incidence of retarded children, and evidences of cerebral injury among the group that really was slow to gain a 90 per cent saturation.

We have to consider the two extremes. The vast majority of those babies, 85 per cent of them, had a saturation that was somewhere in between the two extremes, and there are no significant differences unless the levels are quite marked.

DR. SHIELDS (Closing).—In answer to Dr. Kantor's question about prolonged studies with the oximeter, we did, in a few cases, particularly those following cesarean section. We found that once the saturation level reached 90 per cent or above, it ordinarily stayed at this level from then on. We followed some for a matter of three hours, and after they reached additional levels of 90 per cent, they either stayed there or improved.

Dr. Dieckmann cautions us that oxygen is a poison. I know that oxygen is a poison. Oxygen does damage the guinea pig's lungs, but it doesn't bother the guinea pig's lungs until it has been exposed to high concentrations of oxygen for at least 24 or 32 hours or above. Brief periods of 100 per cent oxygen caused absolutely no damage that we could determine, at least with the guinea pigs, and in human experiments nobody has reported any damaging effect of 100 per cent oxygen until it has been prolonged for a period of longer than 24 hours.

We also found that if oxygen is administered in percentages of less than 60 per cent, it is not toxic at sea level pressures. Sixty per cent certainly should be adequate to get most newborn infants past their immediate difficulties.

Then he asked as to the error of the oximeter. We have used the chemical method of blood oxygen determination, and we have used the oximeter. The oximeter has its greatest inaccuracy above 90 per cent; it has its greatest accuracy below 90 per cent. From a practical standpoint, we are interested in the low saturation levels, and are not particularly interested in the small fluctuations at the higher levels, so, at least for this experiment, the oximeter was ideal, because we could get direct and continuous readings of the arterial saturation levels without having to obtain blood samples every two minutes.

Dr. Randall brought up the question of relatively small changes in the oxygen saturation levels. We are not impressed with relatively small changes in oxygen saturation levels. These studies merely show a qualitative and not a quantitative representation of the oxygen saturation level following the delivery. All they do is give us trends in the saturation levels, and certainly, we are not going to quibble over the difference between 5 and 10 per cent of an oxygen saturation level, or make any fantastic predictions,

## ETIOLOGICAL APPROACH TO HABITUAL ABORTION\*

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THERE are numerous articles on the management of threatened and habitual abortion in the recent literature.<sup>1-5</sup> The multiplicity of therapeutic approaches attests the current confusion surrounding the numerous techniques of evaluation and treatment. Despite advances in our understanding of the physiologic and endocrine changes of pregnancy, the preservation of any threatened pregnancy remains a problem shrouded in mystery. Even more obscure is the approach to habitual abortion, a problem which both physician and patient consider with extreme pessimism. Several different therapeutic regimes have been advocated, each reportedly capable of protecting the threatened pregnancy. From a fetal salvage point of view, the recent reports of Javerts<sup>6</sup> have been the most optimistic presented to date. Previously, serious doubt had been cast on the efficacy of any formal treatment in repeated abortion aside from the general measures of rest, sedation, and adequate nutrition.

In a recent review of the literature, King<sup>7</sup> emphasized the marked variation of cure rate following any one specific form of treatment. He noted that it was virtually impossible to compare statistics from one report to the next, due to different criteria as to the number of sequential losses necessary to establish a diagnosis of habitual abortion. He further pointed out that the present uncertainty in dealing with the repeated aborter was leading to a "philosophy of therapeutic nihilism" which is deleterious to both the profession and the patient. It is the purpose of this paper to divide the evaluated group of habitual aborters into its basic physiologic components purely from the maternal point of view. The management of this problem will then be discussed from an etiologic point of view.

Prior to undertaking any discussion, it is obviously necessary to clarify and define accurately the terms employed. As stated by Crowder,<sup>8</sup> an abortion refers to the detachment or expulsion of an ovum of less than twenty weeks' gestation. Habitual abortion, following Eastman's suggestion,<sup>9</sup> is a sequential loss of pregnancy in which at least three consecutive abortions have occurred. As noted by Benson,<sup>10</sup> habitual aborters are not sterile in their ability to conceive, but cannot carry a fertilized ovum to viability. They therefore represent a group with so-called "pseudo-sterility." Management of these cases in several clinics is and should be an integral part of an infertility service.

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A large portion of our previously held knowledge of the etiology of abortion has been obtained from study of the aborted products: in other words, our investigation of this question has frequently been from purely the fetal rather than the maternal point of view. A blighted ovum either completely lacking or markedly defective in development was described by Hertig<sup>11</sup> in 48.9 per cent of cases studied. Zygotic changes inconsistent with further embryonic development were revealed in 61.7 per cent of the evaluated cases. In a series of 440 threatened abortions, Colvin and associates<sup>12</sup> attributed 72.2 per cent of the cases to blighted products of conception. This figure is somewhat higher than usually reported but stresses the abnormal embryonic development previously considered of importance in the causation of abortion. Despite these impressive figures, it is vitally important to note, as pointed out by Furuhjelm,<sup>13</sup> that pathologic changes in the ovum may be not only of primary origin but also secondary to faulty implantation or poor nutrition, both of which may well hamper natural development of an ovum. An absolute causal relationship, therefore, is certainly not established in cases of habitual abortion when the products of conception are subsequently reported to show evidence of abnormal development.

The importance of the male factor in producing an abnormal embryo has received some consideration. Israel<sup>14</sup> stated that a semen specimen containing more than 30 per cent morphologically abnormal forms indicates defective spermatogenesis. Such a specimen may well be incapable of normal fertilization. A report by Grant<sup>15</sup> indicated that 53 per cent of husbands of women subject to chronic abortion displayed a "high instance" of abnormal spermatozoa. These factors indicate the need for careful evaluation of the male element in these cases. There is, however, no proved causal relationship between abnormal spermatozoa and the etiology of multiple abortion. The fact that abnormal spermatozoa will fertilize the human ovum has not been established.

General disturbances of metabolic, nutritional, or toxic origin have likewise been incriminated as maternal factors in causation of abortion. Systemic diseases and malnutrition have received increasing attention, especially in reports from Europe on the effect of starvation on maintenance and outcome of pregnancy. The roles of the Rh factor and blood grouping incompatibility appear to be unimportant. Severe vitamin deficiencies, primarily of vitamins B, C, E, or K, have been incriminated experimentally as the causes of early abortion; however, it is unlikely that deficiencies of such experimental magnitude ever occur in man.

Two types of habitual aborters have been seen by the Infertility Service at Washington University. First in frequency, and termed "primary aborter" is the couple who have never carried a pregnancy to term. To be considered in the multiple aborter group, the family unit must have sequentially lost at least three established pregnancies. Second, but in surprising numbers, is the "secondary aborter" group. This is the family unit which has taken one or more pregnancies to or near to term, but have then lost in succession at least



three subsequently established pregnancies. The problems of these two groups obviously overlap when the etiology of abortion is considered. However, individual group causation may be quite definitive, and an essential difference between the two aborter groups is easily established if maternal factors alone are considered.

A total of 29 multiple aborters have been evaluated by the Infertility Service. This series is comprised of 19 members of the primary aborter group and 10 members of the secondary aborter group. In addition, another 12 unclassified habitual aborters have been empirically treated, or are in the process of pregnancy support.

TABLE I. ETIOLOGY OF HABITUAL ABORTION (TWENTY-NINE CASES)

	PRIMARY ABORTER*	SECONDARY ABORTER†	TOTAL
Endometrial fibrosis	9	8	17
Didelphic uterus	5	0	5
Etiology unknown	5	2	7
	19	10	29

\*Primary aborter is defined as one with the sequential loss of at least three established pregnancies by the end of the third month of gestation without previous history of term or near-term pregnancy.

†Secondary aborter is defined as one with the sequential loss of at least three established pregnancies by the end of the third month of gestation, subsequent to one or more term or near-term pregnancies.

As described in Table I, a definitive diagnosis of endometrial fibrosis has been established in 17 of the 29 cases of multiple abortion. There are an additional 5 women (all members of the primary aborter group), in whom a didelphic uterus was demonstrated. In 3 of these patients a significant degree of endometrial fibrosis was also present.

The investigation did not successfully define maternal etiology in the remaining 7 women in the series. Thus, in 22 of 29 cases, a definitive explanation for the patient's multiple abortion problem has been established. The problems of endometrial fibrosis and uterus didelphys will be presented and discussed in order.

Endometrial fibrosis concerns both the primary and secondary aborter groups, a total of 17 women having an established diagnosis. The diagnosis is usually arrived at by a combination of definitive past history and examination of the results of endometrial biopsy techniques and of diagnostic curettage.

The focal point of significance in the past history is postpartum infection. Any history of postpartum or postabortal infection may well be the prime clue in the detection of endometrial fibrosis. It is true, of course, that at least half of the patients who have suffered a severe postpregnancy infection will not be able to provide a positive history of the morbid episode. A positive history of criminal abortion was obtained in only 2 of the 19 members of the primary aborter group. Careful questioning in the direction of excessively long hospital stay, positive knowledge of the use of antibiotics or sulfonamides, or long-maintained foul vaginal discharge may turn up suggestive hints of a previous infective postpregnancy complication.

Fig. 1.—An advanced degree of endometrial fibrosis. Note compression and relative loss of function of endometrial glands. Usual tissue edema and vascularity of premenstrual phase of cycle are absent. The section is markedly avascular. ( $\times 115$ ; reduced  $\frac{1}{4}$ .)

Fig. 2.—Another example of advanced endometrial fibrosis. Free tissue strands in one corner of the section. The glands are compressed and even invaginated in several instances. Stromal edema of the terminal luteal phase of the cycle is absent. Marked avascularity is noted. ( $\times 115$ ; reduced  $\frac{1}{4}$ .)

Fig. 3.—A moderate degree of endometrial fibrosis. Fibrous tissue strands demonstrable in avascular stroma. Luteal tissue edema is absent. Glands do, however, demonstrate secretory activity. The stroma is obviously unaffected by progesterone influence. ( $\times 115$ ; reduced  $\frac{1}{4}$ .)



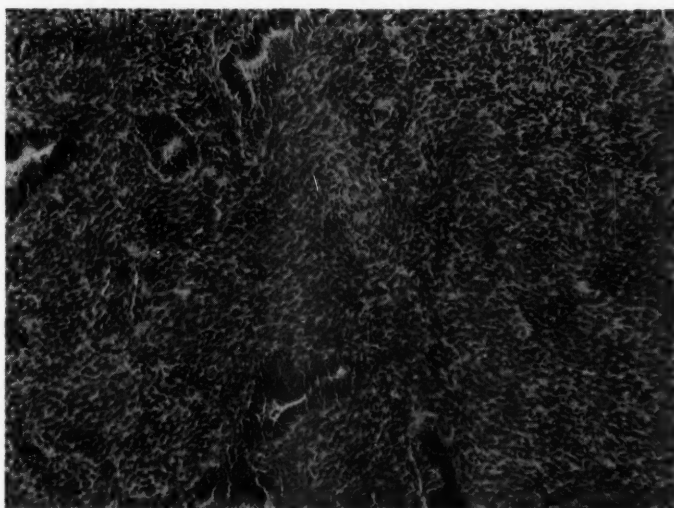


Fig. 1.

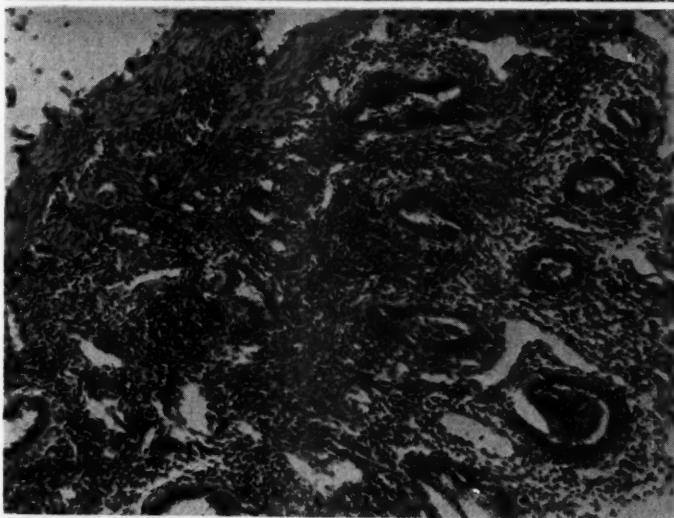


Fig. 2.

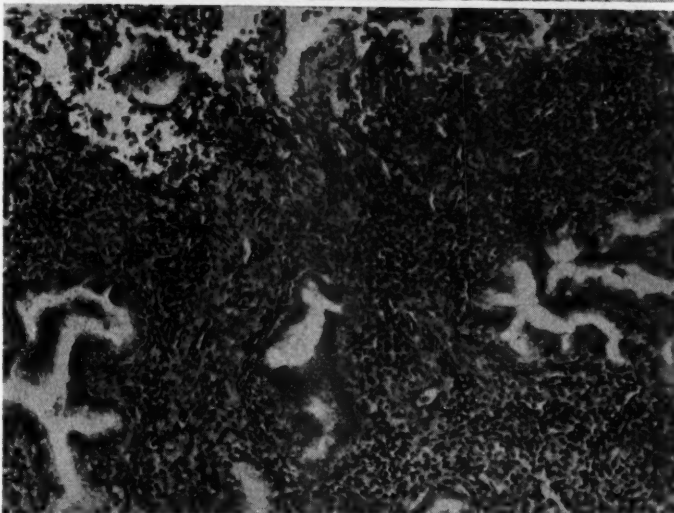


Fig. 3.

Figs. 1-3.—For legends see opposite page.

Suggestion from the past history of present endometrial fibrosis may also be obtained from careful examination of the patient's menstrual history. Many patients have noted a major difference in the pattern of their periods subsequent to significant postpregnancy endometrial infection. Following such an unfortunate episode, the previously established normalcy of menstrual pattern may be markedly changed. Instead of the usual four-to-six-day duration of flow, and the established normal intensity of flow, the patients will frequently describe a short two-to-three-day menstrual period and/or a significant reduction in the amount of flow.

The endometrial biopsy is an absolute necessity during the clinical evaluation of the multiple abortion problem. With a return of sufficient endometrial tissue, a diagnosis of endometrial fibrosis may be either established or strongly suspected. The degree of fibrosis varies from patient to patient and, interestingly enough, within the individual uterine cavity.

In advanced cases (Fig. 1) the endometrial stroma has a fibrous content far in excess of normal. The stromal edema associated with the late luteal phases of the menstrual cycle usually does not occur. Endometrial glands are markedly compressed. In fact, few glands may be demonstrated and their secretory activity is obviously depressed. The lymphocytic infiltration always present in the lesser degrees of fibrosis may be absent. Of particular moment is the marked degree of avascularity of the section.

A second example of severe fibrosis is demonstrated in Fig. 2. Free bands of pure fibrosis tissue may be noted in one part of the section. The basic stroma and a minor degree of tissue edema are demonstrable. Endometrial glands are present in increased numbers although compression of glandular lumina and thickening or bunching of the normal columnar epithelium are easily discerned. Avascularity is still of major moment.

A moderate degree of fibrosis is exemplified by Figs. 3 and 4. Patches of fibrous tissue are easily discerned. The usual chronic round-cell infiltration is freely pictured. The stroma has patchy integrity, and the glandular patterns are relatively within normal limits.

A minimal degree of fibrosis is exemplified by Fig. 5. Here the normal stromal edema and integrity are easily demonstrated. Glandular patterns are completely within normal limits. However, patchy round-cell infiltration and fibrosis are also easily noted. This is a typical picture of a reconstituted endometrial stroma, after therapeutic curettage in a moderate or severe case of endometrial fibrosis.

The typical radiological pattern of didelphic uterus is presented in Fig. 6. The dual-horned uterus was found to be present in 5 of the 19 investigated primary aborter patients. It is of interest that this developmental anomaly was not demonstrated in any of the 10 cases of the secondary aborter series.

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Fig. 4.—A moderate degree of endometrial fibrosis. Stromal thickening with loose fibrous tissue bundles is clearly demonstrable. The usual round-cell infiltration of moderate or lesser degrees of endometrial fibrosis is present. Glands are in active secretory phase. Moderate compression of the lumina is seen. There is a modest degree of avascularity in this section. (X115; reduced  $\frac{1}{2}$ .)

Fig. 5.—Minimal endometrial fibrosis is present in this section. Tissue is endometrial biopsy taken two months after therapeutic curettage of patient with severe fibrosis (Fig. 2). Many fibroblasts are still present in the stroma. The usual chronic round-cell infiltration is noted. However, the stroma has lost the compact fibrotic form. Blood vessels are present throughout the section. Glands are not compressed by stroma. Section taken in nonsecretory phase of the menstrual cycle. Patient carried pregnancy to term within a year after this biopsy. (X115; reduced  $\frac{1}{2}$ .)

Fig. 6.—Typical didelphic uterus with common cervix as demonstrated by salpingogram technique. Tubal patency demonstrated in this and further plates in this series. Patient had lost 4 sequential conceptions as a primary aborter. Carried to term with progesterone support.

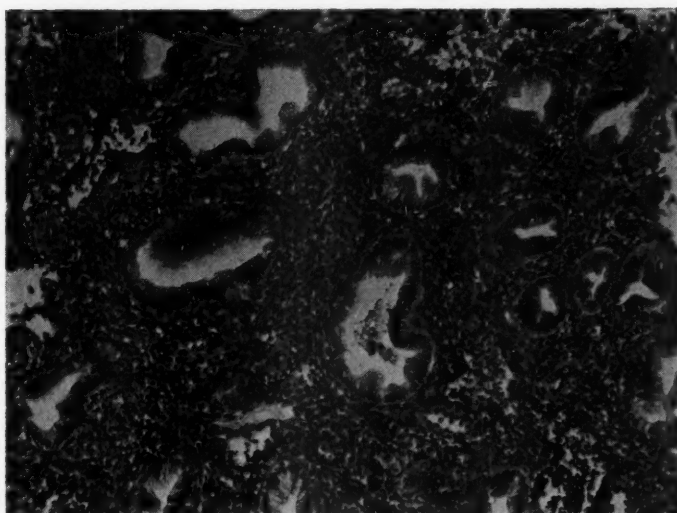


Fig. 4.

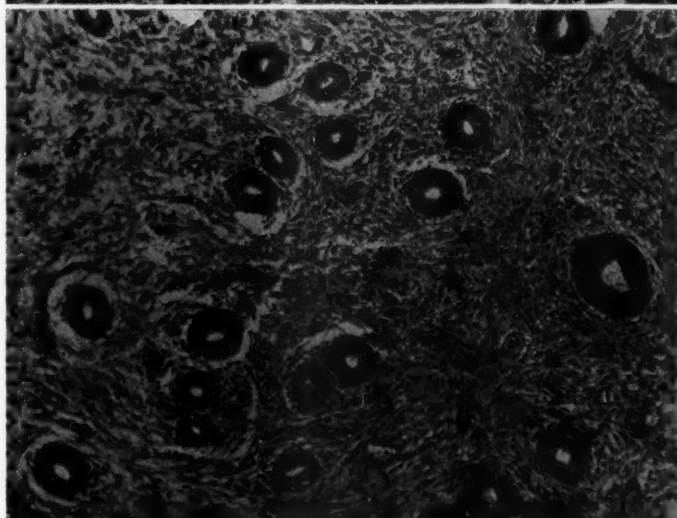


Fig. 5.



Fig. 6.

Figs. 4-6.—*For legends see opposite page.*

A brief description of the semen analysis of this marital partner should also be included in this report. Despite suggestive reports such as Grant's,<sup>15</sup> complete semen analysis of all husbands in the multiple aborter series (29 in all) showed only one male with an abnormal sperm count that reached a level of 10 per cent abnormal forms. This particular abnormality immediately responded to indicated thyroid therapy (B.M.R.—minus 20) and could not be further indicted despite his partner's two subsequent abortions. (This particular multiple abortion problem is listed in the "etiology unknown" column.)

### Comment

The question of habitual abortion is explained on the basis of previous puerperal infection in better than 50 per cent of the investigated cases. Of course, positive history of previous postpartum or postabortal infection could not be established in all cases investigated. Suggestive positive history is obtained from changes in established menstrual patterns subsequent to a particular gestation. If the length of flow is diminished, and/or the amount of flow significantly decreased from the patient's previous established normal picture, a diagnosis of endometrial fibrosis should be entertained.

A routine endometrial biopsy will usually return sufficient tissue to support a diagnosis of endometrial fibrosis. Armed with a biopsy specimen positive for fibrosis, a definitive and, at the same time, therapeutic curettage should be carried out. The curettage must be especially severe in character. Every attempt should be made to remove the fibrotic endometrium. To achieve success by this technique, it is necessary to include a good portion of the basalis layer of the endometrium in the curettage. The patient should be thoroughly protected by wide-spectrum antibiotic therapy before and after the operation. Needless to say, the previously established chronic infectious process will probably be reactivated during the surgical procedure, and at this time will be most amenable to antibiotic therapy.

All of the 17 cases of endometrial fibrosis were subjected to the therapeutic curettage technique. In 10 of these patients, there was marked reduction in the degree of fibrotic involvement with regrowth of the endometrial stroma. It is interesting to note in Fig. 5 that the normal stromal edema and uncompressed glandular pattern have been reconstituted. A moderate round-cell infiltration is still present. There is still a mild stage of endometrial fibrosis, but when Fig. 5 is compared to Fig. 2, the results of therapeutic curettage are clearly established.

It is important to emphasize that the curettage should be severe enough in character to include a major portion of the basilar portion of the endometrium. In other words, the endometrial tissue loss should be much more severe than that associated with usual menstrual wastage. A concern for lack of endometrial regrowth subsequent to real insult of the basalis layer is acknowledged. So far, there has been no such instance in the patients subjected to the therapeutic curettage procedure.

There was no discernible reduction in the degree of endometrial fibrosis subsequent to therapeutic curettage in 7 of the total of 17 patients in whom the diagnosis was established, and who were subjected to the therapeutic curettage technique. When the endometrium was reconstituted from the remaining basalis layer, the fibrotic character of the endometrium was to all intents and purposes unchanged. These 7 patients have also defied further therapy to date. Recurettement of 2 of the 7 patients did not result in significant change in the endometrial pattern. In one instance, topical applications of cortisone during three successive menstrual periods in an effort to



check the fibrotic reaction process in the newly constituted endometrium were also unsuccessful. However, this technique is at present under further investigation.

In the presence of moderate to severe endometrial fibrosis, the fundamental concern in satisfactory pregnancy support is the concomitant avascularity of the endometrial stroma. The blood vessel patterns are poorly developed. The normal stromal edema, the glandular hypertrophy and secretory activity, so vital for successful support of a nidation site, do not occur. Vessels are pinched and glandular lumina are flattened in many instances to the point of atrophy. An essentially unstimulated endometrium is the common picture. In essence, the typical progestational influence on the endometrium, so vital for successful implantation and protection of the fertilized ovum, does not occur. This unstimulated endometrium is produced in spite of the fact that by vaginal smear every case of endometrial fibrosis has demonstrated a good luteal effect on the vaginal mucosa. A uterine endometrium sufficiently disturbed by the results of a previously morbid postgestational infectious episode will not respond effectively to the normal amounts of progesterone produced by the usual corpus luteum of pregnancy.

The didelphic uterus has been of unusual interest in the habitual abortion problem. Complete reduplication of the uterine cavity with a common cervix is demonstrated in Fig. 6. The problem of the excessively small uterine cavity and questionable integrity of the lower uterine segment is clearly demonstrated. In the present series this pathology has been confined to the primary aborter group, where 5 of the 19 group members have been shown to have anomalous uterine cavities. During the course of their multiple abortions, 3 of the 5 women with didelphic uteri became sufficiently infected to develop secondarily a moderately advanced endometrial fibrosis, thus adding significantly to their basic distress. (These 3 cases are listed solely in the didelphic uterus column, and not secondarily under the heading of endometrial fibrosis.)

In this particular situation, the small or incomplete uterus apparently does not satisfactorily respond to the tremendous demand for rapid muscular hypertrophy and secondary cavity expansion. In a hypertonic uterus, nidation sites are either not satisfactorily supported, or are frequently completely expelled prematurely. If infection occurs subsequently to any abortive episode, the pathologic condition of endometrial fibrosis may well be added to the already gloomy picture.

A routine curettage is carried out on all patients with a didelphic uterus. The integrity of corporal walls is investigated as well as possible. If endometrial fibrosis is suspected, the therapeutic curettage techniques previously described are rigorously carried out. The cases of didelphic uterus also represent a clinical picture of insufficient progesterone. The small or incompetent endometrial cavities are frequently not capable of successfully supporting a nidation site. As previously described, sufficient true decidua may not be developed from the scanty normal stroma or excessive uterine muscular tension may shear off or partially separate an implanted ovum during hyperactive uterine contractile phases.

### Treatment

The basic rationale for treatment of the multiple abortion problem has been to oversupply progesterone influence to the maternal organism at the theoretical implantation time, and to support the nidation site in like manner through the entire course of the pregnancy. The therapeutic curettage has also been used as described in cases of moderate or advanced endometrial fibrosis. Of the 17 cases subjected to this technique, in 10 the endometrium was regenerated with a significant reduction in the previously described degree of fibrosis. Whether

or not the endometrium responds to the therapeutic curettage technique, all patients are protected by extraneously increased progesterone influence when subsequently undertaking controlled pregnancies.

If a patient is presumed to ovulate regularly as demonstrated by vaginal smears and temperature charts, progesterone support is instituted roughly 48 hours after ovulation and conception are presumed to occur. Progesterone linguets have been used. The dosage has been from 10 to 25 mg. per twenty-four hour period, depending upon the severity of the previously diagnosed endometrial fibrosis.

It is recognized that a normal menstrual period may be delayed and pregnancy simulated by a dosage of progesterone as high as 25 mg. per day in linguet form. This is a risk that must be accepted, if successful implantation is to be encouraged. Patients are warned that a delayed period may not mean pregnancy, and in all instances (including the 3 simulated pregnancies from excessive progesterone influence) have been most cooperative, when they understood the rationale behind their treatment.

If the patient reaches the thirty-fifth day of amenorrhea, parenteral progesterone therapy is instituted. This technique is carried out without sure knowledge of pregnancy. Intramuscular hydroxyprogesterone caproate therapy, 125 mg. per day, is maintained through the fourth missed period. (Needless to say, a state of pregnancy is diagnosed as soon as possible.) If cramping or bloody discharge occurs, the patient is hospitalized and the hydroxyprogesterone caproate (H.P.C.) dosage is at least doubled.

In the endometrial fibrosis group of multiple aborters, the dosage is reduced to biweekly injections of 125 mg. of H.P.C. after the fourth missed menstrual period. The patients are carried to term on this dosage unless miscarriage or premature labor threatens. In such a situation massive H.P.C. therapy would be instituted immediately. Presently, several patients are in the course of a pregnancy, unsupported by supplementary H.P.C. therapy past the fourth missed period. These cases are too few and too recent to warrant more than mention here. It may well be that supplementary H.P.C. dosage past the theoretical onset of major placental influence is unnecessary.

In the cases of didelphic uterus, therapy has been continued at dosage levels of 125 mg. or 250 mg. H.P.C. a day from the thirty-fifth day of pregnancy to the end of the eighth month. This change in technique and especially heavy H.P.C. protection is a purely empirical attempt to counteract the well-known tendency toward miscarriage or premature labor on the part of those patients who have relatively incompetent uteri.

### Results

The results of the aforementioned therapeutic regime are incomplete at present. Several patients are still in the process of pregnancy support, although well past the fourth missed period. However, a brief summation of present data is in order.

A review of Table II will recall the fact that there are 17 habitual aborters in the endometrial fibrosis group. Ten of these patients responded to the therapeutic curettage regime, and 9 of these 10 patients, supported additionally by the techniques of H.P.C. administration previously described, have subsequently carried at least one pregnancy to term. From the remaining 7 fibrosis cases, only 2 patients (apparently unaffected by the therapeutic curettage technique but H.P.C. supported as described) have also carried at

least one pregnancy to viability. Thus, 6 of the original 17 endometrial fibrosis cases must be listed as treatment failures since they have been unable to support pregnancies to a period of viability while under supervision of the infertility service.

TABLE II. RESULTS OF TREATMENT

	PRIMARY ABORTER	SECONDARY ABORTER	TOTAL
Endometrial fibrosis	9	8	17
Regeneration of afibrotic endometrium after curettage	6	4	10
Pregnancy to viability*	5	4	9
Fibrotic endometrium unaffected by curettage	3	4	7
Pregnancy to viability*	1	1	2

\*All pregnant patients subjected to hydroxyprogesterone caproate support.

Three of the 5 patients with didelphic uteri (Table III) have also carried subsequent conceptions to a period of viability. These patients have usually been delivered from the thirty-fifth to the thirty-seventh week of gestation while under the control methods previously described. One of the 2 failures in this group also has a severe degree of endometrial fibrosis which did not respond to curettage. Thus, 14 of the 22 patients in whom the etiology of habitual abortion (maternal in origin) could be established have ultimately known pregnancy success.

The results in the "etiology unknown" group have been disheartening. Seven patients were in this category (Table III). Only one patient has succeeded in attaining a near-term pregnancy. This was under heavy H.P.C. support (250 mg. intramuscularly each day). She has, however, subsequently aborted 2 successive pregnancy attempts. In essence, there is something grossly wrong in this group of patients that the infertility investigation has not described. The miserable results in this group as compared to the successes in the fibrosis and didelphic uterus cases point out the continued inadequacies of the evaluation of the habitual aborter at present writing. It may well be that contained in this minority group of cases are some individuals with primary anomalies of ovum development.

TABLE III. RESULTS OF TREATMENT

	PRIMARY ABORTER	SECONDARY ABORTER	TOTAL
Didelphic uterus	5	0	5
Pregnancy to viability*	3	0	3
Etiology unknown	5	2	7
Pregnancy to viability*	1	0	1

\*All pregnant patients subjected to hydroxyprogesterone caproate support.

It should be noted in passing that 12 habitual aborters have been referred to the infertility service in very early stages of pregnancy. Of course, the established state of pregnancy precluded a definitive diagnosis of possible maternal etiological factors. In 6 instances, loss of the pregnancy was already threatened at the time of referral. All patients have been empirically placed on the heavy H.P.C. supportive techniques previously outlined. Seven of the



12 members of this group have now passed the seventh month of gestation. This salvage rate emphasizes the value of overwhelming progesterone support in the early stages of pregnancy in patients who are habitual aborters.

It becomes increasingly obvious that the primary approach to the habitual abortion problem should be fundamentally from the maternal etiological point of view. In the majority of cases investigated, a definitive diagnosis was established and steps taken to correct the basic maternal defect.

The usual defeatist attitude on the part of both physician and patient is certainly not warranted by the information presently available. It is obvious that the frequently held medical opinion that multiple abortion situations are the result of primary ovular or spermatic anomalies is in complete error. All of the evidence presented supports the contention that the high percentage of developmental anomalies encountered, when the products of conception are examined postabortionally, are secondary to lack of proper physiological support of the nidation site. It is also obvious that there is a significant pregnancy salvage rate available to habitual aborter patients, if the investigating physician will concentrate on the basic problem of maternal etiology when treating these seriously distressed individuals.

### Summary

The maternal etiological components in a series of 29 habitual aborters have been defined in 22 cases. Endometrial fibrosis was present in 17 patients, and a didelphic uterus was found in the 5 remaining individuals. The techniques of diagnosis and treatment for these pathological entities have been described and discussed. All evidence presented supports the contention that the fetal developmental anomalies so frequently associated with habitual abortion are secondary to poor physical support of, or inadequate nutrition at, the nidation site, rather than to a primary failure of embryonic development.

We wish to express our deep appreciation to E. R. Squibb & Sons and to their Associate Medical Director, Dr. Edward C. Reifenshtein, Jr., for their complete cooperation in making available the unlimited supply of 17-alpha-hydroxyprogesterone caproate, Delalutin, necessary to carry this project to completion.

### References

1. Bevis, D. C. A.: *Lancet* 2: 207, 1951.
2. Mauzey, A. J.: *Illinois M. J.* 98: 116, 1950.
3. McGoogan, L. S.: *J. Omaha Mid. West Clin. Soc.* 12: 40, 1951.
4. Snaith, L.: *Glasgow M. J.* 33: 286, 1952.
5. Furuhjelm, M.: *Acta obst. et gynec. scandinav.* 29: 407, 1950.
6. Javert, C. T.: *Obst. & Gynec.* 3: 420, 1954.
7. King, A. G.: *Obst. & Gynec.* 1: 104, 1953.
8. Crowder, R. E., Bills, E. S., and Broadbent, J. S.: *AM. J. OBST. & GYNEC.* 60: 896, 1950.
9. Eastman, N. J.: Editorial Comment on Habitual Abortion, *Obst. & Gynec. Surv.* 2: 17, 1947.
10. Benson, R. C.: *California Med.* 72: 942, 1950.
11. Hertig, A. T., and Livingston, R. G.: *New England J. Med.* 230: 797, 1944.
12. Colvin, E. D., Bartholomew, R. A., Grimes, W. H., and Fish, J. S.: *AM. J. OBST. & GYNEC.* 59: 1208, 1950.
13. Furuhjelm, M.: *Acta obst. & gynec. scandinav.* 28: 92, 1949.
14. Israel, S. L.: *Am. Pract. & Digest Treat.* 1: 381, 1950.
15. Grant, A. G.: *Fertil. & Steril.* 4: 169, 1953. (Correspondence.)



### Discussion

DR. ROBERT W. McCLURE, Detroit, Mich.—This timely subject is controversial because of the multitude of therapeutic agents and regimes, with comparable degrees of success, all pointing to the distinct possibility that the lowest common denominator is a maternal malfunction.

As Dr. Masters has pointed out, most authors, in explaining the maternal factor, aside from stress and the psychological etiological factors of repeated abortion, which most regimes subconsciously or deliberately treat in varying degree, localize the malfunction in the decidual area of the uterus, and it, in turn, is dependent upon luteinizing hormones for competence. The treatment is variously directed toward vitamin deficiency, thyroid deficiency, progesterone augmentation, and the recognition of mechanically unfavorable conditions. But, as Dr. Masters stated, "The preservation of a threatened pregnancy remains a problem shrouded in mystery."

I find it difficult to picture a pregnancy in a uterus containing the severe avascularity and fibrosis he suggests. Rather, I see a sterile patient. In the less severe cases it could possibly account for the incidence of silent abortion set by Hertig and Rock at 20 per cent of all gestations in the only reliable study of this condition.

My own patients with threatened abortion have been treated for a period of six or seven years with sulfonamides and antibiotics, with sulfonamides by mouth and the liberal use of the telephone. This regime was satisfactorily followed in primary or secondary habitual aborters who threatened to abort. Two had a uterus didelphis; only one had a metroplasty, and carried to term on two occasions, the first of which presented the threat. This, in spite of the full knowledge that Hertig and Livingstone, commenting on the studies on abortion by Mall and Myers in 1921, mentioned the small part local inflammation plays in abortion, and their observation that Mall and Myers misinterpreted the leukocytic response to sterile decidual necrosis following thrombosis of the sinusoids.

Mary Barton, in the Royce Free Hospital, London, cleared up 35 cervices with chloramphenicol, and is inclined to believe that even minor infections may cause sufficient toxemia to affect ovarian function directly or indirectly.

It has been shown that pregnancies which do not show a high-level temperature in the luteal phase tend to be aborted, but rises have been reported following the use of chloramphenicol.

Jeffcoate states flatly that stilbestrol or progesterone does not prevent abortion. Javert has utilized vitamins C, K, and P to keep the sinusoidal bleeding from becoming excessive to the point of terminating the pregnancy by anoxic change in the fetus, or mechanical disruption sufficient to lead to abortion.

I wish to ask Dr. Masters if he feels that a prophylactic curettage and antibiotic therapy should ideally be done after every abortion as a prophylactic measure.

DR. MASTERS (Closing).—As I pointed out in the course of the paper, at present we are in a small series of such cases, primarily concerned with etiology. All of the reports that were mentioned by the discussant were primarily concerned with results. These cases are certainly too few to be of any statistical value as far as results are concerned, which is the reason the results are not emphasized this morning.

The whole secret, so far as we are concerned, is that habitual abortion is shrouded in mystery, primarily because we have not aimed, from an investigating point of view, to find out the cause.

This is simply to supplement what has been done previously, in that we are honestly trying to present—at least, in theory, we are—what are reasonably established etiological factors in the cause of habitual abortion.

In answer to one question that was raised by the discussant—do we feel that this endometrium may be simply unstimulated as opposed to an opportunity for previous infection?—no, we do not. Relative proof of the pudding in this particular situation is the fact that with substitutive therapeutic curettage, in the patient with early minimal severe fibrosis, when the endometrium was regenerated in the same individual, and without any

change whatever in her basic humoral pattern, she was able to maintain a relatively normal endometrium. Here was an individual who had a basically normal humoral system, so far as we could tell, on repeated evaluation. Subsequent to therapeutic curettage, an adequate endometrium was maintained. The pattern of flow, and duration, went back to normal. This occurred in 10 cases.

The basic and big question is: Do we recommend routine curettage in all cases of incomplete or even threatened abortion? Naturally, not. Certainly, there are many patients who can adequately expel the product of conception without either exceptional bleeding or any of the sequelae that go with it. Certainly, we do suggest that any individual who is being allowed to bring to a conclusion her particular abortion problem should be covered with antibiotic therapy to prevent, as far as possible, the onset of a picture such as we described.

However, if an individual, in the process of trying to extrude the no longer viable product of conception, continues to spot and bleed for X number of days, then, by all means, we suggest curettage, again covering the individual with antibiotic therapy.

Probably the most important thing is the coverage with antibiotic therapy during the time the individual is either threatening or is actually trying to extrude the product of conception.

## HYSTERECTOMY ON GRAVID PATIENTS\*

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ANOTHER paper on the subject of hysterectomy would appeal to very few readers. There are problems associated with the pregnant patient, however, that are not encountered in the nonpregnant woman. It is this group of patients who produce many of the emergencies requiring prompt, effective, and, at times, heroic treatment. This apparent urgency may color decisions that will look different in the calmer atmosphere of the reviewing committee. This report is the result of a review of hysterectomy done on the gravid patient or on patients in the immediate postpartum period. This includes diagnosed and undiagnosed pregnancy, therapeutic abortion, ectopic (tubal) pregnancy, complications of pregnancy, labor, and the puerperium.

### Material

The records of University Hospital, both for the department of obstetrics and gynecology and the department of surgery, were reviewed for the fifteen-year period 1940-1954. The records from the department of surgery were all of private patients. One hundred seventy-five patients were found to be pregnant or to have just finished a term pregnancy at the time of operation. These were classified into groups as indicated in Table I for convenience in discussing the various problems.

TABLE I. CLASSIFICATION OF CASES

Number of deliveries		58,606
Number of cesarean sections		3,953
Cesarean section hysterectomies	58	
Postpartum hysterectomies	18	
Hysterectomy near fetal viability	2	
Incidental to other pathological conditions	2	
Pregnancy not diagnosed	10	
Pregnancy diagnosed but operation performed	7	
Therapeutic abortion	31	
Tubal pregnancy	39	
Tubal pregnancy, not diagnosed	7	
Tubal pregnancy, diagnosed, error	1	
Total	175	

**Cesarean Section Hysterectomy.**—The term cesarean section hysterectomy is used here to include hysterectomy done at the time of a cesarean section or in the immediate postpartum period. There were 76 patients in this group. Table II gives the status, race, parity, and age. It will readily be noted that 36, or 47.3 per cent, of the patients were in the age group of 35 to 45 years. Twelve per cent of the patients were in their fifth to eighth pregnancy. There

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were over twice the number of hysterectomies in the white group and almost twice the number done on the private service. This is in contrast to the usual thinking that the staff patient has the greater pathology and complications of pregnancy. It might indicate that the private physician is hesitant to take any undue chances with his patient. There is usually more than one physician involved in the decisions concerning the staff patient and sometimes a longer interval of observation and treatment elapses before the final decision is made.

TABLE II. PARITY, AGE, RACE AND STATUS OF 76 PATIENTS WHO HAD HYSTERECTOMIES

	NO. OF PATIENTS
<i>Parity.</i> —	
0	16
i	15
ii	18
iii	11
iv	7
v	1
vi	1
viii	7
<i>Age.</i> —	
20-25	2
25-30	15
30-35	23
35-40	27
40 plus	9
<i>Race.</i> —	
White	53
Nonwhite	23
<i>Status.</i> —	
Private	47
Staff	29

TABLE III. INDICATIONS FOR HYSTERECTOMY

INDICATION	NO.
Fibroids	17
Fibroids with previous cesarean section	4
Cardiovascular disease	7
Previous cesarean section	5
Previous cesarean section and rupture of uterus	2
Previous cesarean section and postpartum hemorrhage	1
Eclampsia	4
Hemorrhage	
Ablatio placentae	5
Placenta accreta	5
Placenta previa	5
Atonic uterus	7
Rupture of uterus	8
Multiparity and previous cesarean section	1
Contracted pelvis	3
Erythroblastosis	1
Herniation of stomach	1

The indications as stated on the records have been listed in Table III. There were multiple indications in a number of cases although an effort was made to report the major indication. Fibroids of sufficient size and particular location accounted for 17 hysterectomies. Previous sections and fibroids were noted in 4 additional cases. The diagnosis of multiparity associated with placenta previa, ablatio placentae, previous section, and eclampsia was noted in 8 patients. Hemorrhage from rupture of the uterus, atony of the uterus, placenta accreta, and ablatio placentae was the main indication for operation in 23 patients. Hemorrhage was also a problem in 10 additional cases, making a total of 33 patients, or 43.4 per cent of the entire group. Hysterectomy was



done on 7 patients with severe cardiovascular disease causing complications of pregnancy necessitating a cesarean section delivery. It was interesting to note that placenta accreta was found in 5 patients. In 3 patients it was a histological diagnosis and in 2 it was responsible for the hemorrhage during the postpartum period.

*Postpartum Hysterectomy.*—Eighteen patients, or 23.6 per cent of the group, were operated upon in the immediate postpartum period. The indications are listed in Table IV. Hemorrhage was a serious problem in 15 cases. Eight patients were in serious shock before the time of operation. The time interval varied from one to eighteen hours from the time of delivery until operation was carried out. One patient in this group had a twin pregnancy with a central placenta previa. Spontaneous rupture occurred before the onset of labor. The weights of the babies were 980 and 1,100 grams. Rupture of the uterus occurred with hemorrhage into the broad ligament in one patient after a version. One rupture followed a precipitous labor and delivery. One patient, a gravida v, was delivered by breech extraction. She immediately went into shock from hemorrhage caused by a degenerating myoma that weighed 2,117 grams. Supracervical hysterectomy failed to control the bleeding. The cervix was clamped from below, later sutured, and finally a second laparotomy was done for the removal of the cervix. The baby weighed 2,970 grams. The patient listed as having an adherent placenta had delivered her fourth child. The obstetrician did an extensive plastic repair while waiting for the placenta to separate. He was unable to deliver the placenta by the usual means and, rather than tear down the repair, elected to remove the uterus. The uterus weighed 740 grams. This patient would not have been operated upon today and certainly the hysterectomy would not have been necessary if the plastic procedures had been delayed until the current complication had been corrected. In one patient, the placenta was so situated behind a large fibroid that it could not be removed. The uterus weighed 2,250 grams. There was one patient in whom hemorrhage after a miscarriage could not be controlled by the usual therapy and finally the physician removed the uterus.

TABLE IV. INDICATIONS FOR POSTPARTUM HYSTERECTOMY

DIAGNOSIS	NO. OF PATIENTS
Rupture of uterus	7
Placenta accreta	2
Atony of uterus	3
Fibroids, degenerating	2
Adherent placenta and fibroids	1
Ablatio placentae	1
Retained placenta, vaginal plastic	1
Postabortal hemorrhage	1
Total	18

TABLE V. PERMANENT STERILIZATION

INDICATIONS	NO. OF PATIENTS
Previous cesarean sections plus rupture of the uterus	8
Prolapse and renal stones	1
Mitral stenosis (rheumatic)	1
Severe cardiovascular disease	7
Fibroids	4
Grand multiparity with pathology	3
Erythroblastosis	1

*Permanent Sterilization.*—The prevention of future pregnancies must be considered in the total care of patients with serious diseases complicating pregnancy. How to accomplish this in accordance with religious beliefs and moral

values of the patient may enter into the choice of operative procedures. This obviously was a factor in this series, though it was not always recorded as such. It was thought to be one of the considerations in 25 cases, or 43 per cent of the cesarean hysterectomies. The indications are given in Table V.

*Hysterectomy Near Viability.*—There were 2 patients operated upon about the twenty-sixth week of pregnancy. One was 41 years old, white, a private patient in her fourth pregnancy. Hypertension and chronic nephritis with atrophy of the kidneys had been diagnosed after adequate study. One wonders why the diagnosis was not made earlier or why the operation could not have been delayed a few weeks longer without increasing the danger to the mother. The risk to the baby in prolonging the pregnancy makes it of doubtful value but there is always the chance that the outcome might have been better than expected. The delay in making a diagnosis often is caused by the tardiness of the patient in reporting to her physician. The second patient was a 36-year-old nonwhite staff patient in her fifth pregnancy. She was operated upon for an abdominal pregnancy and hysterectomy carried out at the time.

*Pregnancy Incidental to Other Pathology.*—There were two patients in this group with sufficient disease to warrant removal of the uterus in spite of the pregnancy. One was a 30-year-old woman about 8 weeks pregnant. She developed an intestinal obstruction caused by a degenerating fibroid. The uterus weighed 605 grams and the pathological diagnosis was necrosis of the fibroid with hemorrhage. The second patient was a gravida ii, 35 years old, 20 weeks pregnant with a poorly differentiated carcinoma of the cecum, ovary, and tube, with metastases to the lymph nodes. This patient had extensive intestinal surgery in addition to that in the pelvis.

*Pregnancy Not Diagnosed.*—There were 10 patients in this group. Four were private patients, evenly divided between the surgical and the gynecological services. The summary is given in Table VI.

TABLE VI. PATIENTS WITH UNDIAGNOSED PREGNANCY

STATUS	YEAR	RACE	PREOPERATIVE DIAGNOSIS	WEIGHT OF UTERUS (GRAMS)	WEEKS PREGNANT
Private	1946	White	Tumor of uterus	680	12
Private	1947	White	Fibroids. X-ray therapy	300	13
Private	1948	Nonwhite	Fibroids, ovarian cyst	950	7
			Pedunculated fibroid	5,000	
Private	1949	White	Fibroids	575	6
Staff	1946	Nonwhite	Fibroids	685	
Staff	1948	Nonwhite	Myomas	125	
Staff	1950	Nonwhite	Myoma of tube, ovarian cyst	265	
Staff	1952	Nonwhite	Fibroids	615	
Staff	1953	Nonwhite	Fibroids	1,060	
Staff	1953	Nonwhite	Myomas		Missed Ab.

Seven of these patients presented fibroids of varying size. The largest was a pedunculated fibroid weighing 5,000 grams with a uterus that weighed 950 grams. One patient had received radiation therapy two and one-half years prior to this admission for fibroids of the uterus. She had a return of vaginal spotting for one month before this admission. The first patient was admitted for pain in the stomach and vaginal bleeding, with a history of menorrhagia for one year. The attending physician indicated a suspicion of malignancy although the house officer had noted in his history that a pregnancy was a possibility. A postoperative urine specimen was sent to the laboratory for a pregnancy test. It confirmed the pathological diagnosis. The uterus contained a myoma measuring 7.5 by 5 by 5 cm. and a 12 weeks' fetus. This type of case

emphasizes the necessity of a very careful history and a thorough physical examination. Any abnormality of the menstrual cycle during the childbearing age should put one on his guard in regard to the possibility of a pregnancy. In case of suspicion, further investigation is always indicated. It is always the mark of a good surgeon to back out when a mistake has been made. It is hard to believe that a uterus weighing about what it should for the duration of the gestation offers very much in the way of tumors.

*Hysterectomy With Pregnancy Diagnosed.*—This group of cases was the hardest to interpret when the records were reviewed. It is conceivable that all of the indications were not recorded in some instances. A margin of error or a mistake in diagnosis is accepted, however regrettable, in the patient who has an undiagnosed pregnancy removed during operation. When a pregnancy is diagnosed and operation carried out intentionally, then there should be sufficient pathology to justify the procedure. Certainly, departmental consultation is a requisite and usually few operations are found justifiable. There were 7 patients in this group. Five were on the private service, 2 on the surgical service, and 3 on the gynecological service. The oldest patient was a 46-year-old woman in her second pregnancy. The uterus weighed 408 grams with tumors which the department of pathology described as 3 to 6 mm. in diameter. The chief complaint had been vaginal spotting. The second patient was 38 years of age, in her first pregnancy, admitted for fibroids. When told that she was pregnant, she stated, "I want the operation done anyway." The uterus weighed 365 grams. The staff patient operated upon at four months was 32 years of age, complaining of a lump in the abdomen. The specimen weighed 1,590 grams. This patient obviously should not have been operated upon at this stage of her pregnancy. This entire group of patients, all operated on before 1945, would not have been operated on under the controls used today. These cases have been summarized in Table VII.

TABLE VII. PREGNANCY DIAGNOSED BEFORE OPERATION

STATUS	YEAR	RACE	PREOPERATIVE DIAGNOSIS	WEIGHT OF UTERUS (GRAMS)
Private	1942	White	Fibroids and pregnancy	650
Private	1943	White	Prolonged menses	240
Private	1944	White	Fibroids and pregnancy	408
Private	1944	White	Fibroids and pregnancy	365
Private	1945	White	Fibroids and pregnancy	360
Staff	1943	Nonwhite	Lump in the abdomen	1,590
Staff	1944	Nonwhite	Fibroids and pregnancy	360

*Therapeutic Abortion.*—Thirty-one patients had hysterectomy performed for the interruption of pregnancy and sterilization. When and if a pregnancy should be interrupted for the health of the mother, then serious thought should be given to permanent sterilization. The exception to this would be for abnormalities of the fetus as in rubella infections during early pregnancy, when interruption of pregnancy is done to prevent abnormalities rather than for the health of the mother. During the fifteen-year period of this study, there has been a marked change in the indications for interruption of pregnancy. It is done today only after departmental consultation. These patients were evenly divided between the private and staff services. Twenty-five, or 80 per cent, were 35 years of age. Ten patients were in their eighth pregnancy. The choice of this procedure has increased in frequency when five-year intervals were compared. These cases are summarized in Table VIII.

The indications for the interruption of the pregnancies have been listed in Table IX. The hazards of increasing age are well shown in this group as 19,

or 61 per cent, of the operations were done for malignancy, hypertensive cardiovascular disease, and rheumatic heart disease. Tuberculosis, diabetes, and epilepsy are not considered indications today. The one patient with two congenitally blind children presented very serious problems to the departments concerned in handling this family. Carcinoma in situ was discovered histologically. This has occurred in another family since the time of this study. When psychiatric reasons are considered, it is felt that it should be a departmental recommendation and not the opinion of any one psychiatrist. This has decreased the number of cases considered for this procedure.

TABLE VIII. THERAPEUTIC ABORTION

	NO. OF PATIENTS
<i>Gravidity.</i> —	
i	2
ii	5
iii	7
iv	4
v	3
viii plus	10
<i>Age.</i> —	
25-30	2
30-35	4
35-40	8
40-45	10
45 plus	7
<i>Five-Year Period.</i> —	
1940-1944	6
1945-1949	12
1950-1954	13

TABLE IX. INDICATIONS FOR THERAPEUTIC ABORTION

	NO. OF PATIENTS
Malignancy	4
Hypertensive cardiovascular disease	12
Psychiatric indications	6
Tuberculosis	3
Rheumatic heart disease	3
Epilepsy	1
Congenitally blind children and carcinoma in situ	1
Diabetes, at age 46	1
Total	31

TABLE X. PATHOLOGICAL CONDITIONS ASSOCIATED WITH ECTOPIC PREGNANCY

DIAGNOSIS	NO. OF PATIENTS
Endometriosis	3
Fibroids	14
Salpingitis	8
Ovarian cyst	1
Instrumental rupture of uterus	2
Multiparity	1
Second ectopic pregnancy	5
No other pathology	12
Total	46

*Ectopic Pregnancy.*—During the fifteen-year period of this study, there were 417 patients with ectopic pregnancy admitted to University Hospitals, 168 cases diagnosed before rupture and 249 diagnosed on admission as ruptured. forty-seven of these patients were subjected to hysterectomy during the operation, 28 to remove pathology in the uterus or adnexa. The diagnosis of ectopic



pregnancy was correct in 39 cases. In 7 cases the ectopic pregnancy was not diagnosed before operation. One patient had an erroneous diagnosis of ectopic pregnancy which was disproved at operation. The list of associated pathological conditions is given in Table X. Five patients had previously been operated upon for an ectopic pregnancy. The shortest interval between operations for tubal pregnancy was six months. One patient had a tubal pregnancy associated with a uterine pregnancy. There were 2 patients with ruptured cornual pregnancies.

*Rupture of the Uterus.*—One of the major acute emergencies of pregnancy and labor is rupture of the uterus. This occurred in 17 patients during the time of this study. In 8 patients, it occurred before labor, in 4 it followed podalic version, and in one it was after a breech extraction. Precipitous labor accounted for the rupture of the uterus in 4 cases. Ten of these patients had a hysterectomy done to control hemorrhage. Table XI summarizes these cases.

TABLE XI. RUPTURE OF THE UTERUS

	NO. OF PATIENTS
<i>Occasion.</i> —	
Before labor (previous section 7)	8
After version	4
Breech	1
Precipitous labor	4
<i>Age.</i> —	
20-25	2
25-30	5
30-35	5
35-40	5
<i>Race.</i> —	
White	13
Nonwhite	4
<i>Status.</i> —	
Private	12
Staff	5

Seven patients had had a previous section before rupture occurred. In 6 of these, a repair of the rupture was carried out. There was one patient with a history of a previous rupture of the uterus. See Table XII for a summary of these patients.

TABLE XII. PREVIOUS SECTION BEFORE RUPTURE

	NO. OF PATIENTS
Rupture after previous section	7
Repair of rupture	6
One previous section	3
Two previous sections	3
Three previous sections	1
Previous rupture	1
Mole	1
Live births	3
Stillbirths	4

### Mortality

In the series of 175 hysterectomies there were 6 deaths. Three occurred in the cesarean section hysterectomy group after a full-term pregnancy. Two of these patients would probably have been saved today with the aid of fibrinogen. Three deaths occurred in the group of hysterectomies done for the interruption of pregnancy. Two of these patients were in very serious condition

at the time of the operation. It is doubtful if any benefit would have been obtained through surgery but as long as they were doomed they felt that they would like the chance of prolonging life if interrupting the pregnancy would help. The patient with epilepsy was a 23-year-old woman who had been in the hospital with status epilepticus. It was thought at that time that the pregnancy was contributing to the situation. She was sent home after the usual stay following surgery. She was readmitted two days later and died suddenly during the first day of her readmission. This was one of the early cases in the study. Probably the convulsions could have been controlled today with the medicine that is available. Table XIII summarizes these deaths.

TABLE XIII. MORTALITY

GRAVIDITY	STATUS	RACE	AGE	DIAGNOSIS	WEIGHT OF BABY (GRAMS)
<i>Cesarean Section Hysterectomy.—</i>					
iv	Private	White	34	Rupture of uterus	3,500
xii	Staff	Negro	38	Polyhydramnios. Ablatio placentae	2,810
i	Private	White	27	Postpartum hemorrhage	4,050
<i>Therapeutic Abortion.—</i>					
i	Private	White	23	Epilepsy	
v	Staff	Negro	33	Recurrent carcinoma of breast	
xi	Staff	Negro	40	Myocardial infarction	

### Summary

One hundred seventy-five hysterectomies done on gravid patients during the fifteen-year period 1940 to 1954, at University Hospitals, Cleveland, Ohio, have been reviewed. These were divided into the following groups for the purpose of discussion: Diagnosed and undiagnosed pregnancy, therapeutic abortion, ectopic (tubal) pregnancy, complications of pregnancy, labor, and the puerperium.

1. Cesarean section hysterectomy was performed on 76 patients at term. Sixteen operations were done in the postpartum period. Forty-five per cent of the patients were over 35 years of age and 12 per cent were gravida v or more. Hemorrhage was a serious problem in 44.5 per cent of the cases. Fibroids of sufficient size to cause trouble were present in 21 patients, or 27 per cent. Eclampsia, placenta previa, and ablatio placentae associated with multiparity were noted in 8 cases. Severe cardiovascular disease was the cause in 7 cases.

2. Permanent sterilization was thought to be a factor in deciding the type of operation in 25 patients. This was noted in patients with serious diseases complicating pregnancy, associated with greater multiparity.

3. Hysterectomy near viability was done in 2 cases, one an abdominal pregnancy and one serious renal disease.

4. Malignancy of the internal genitals and bowel accounted for one operation. Bowel obstruction from a necrotizing fibroid necessitated a hysterectomy in a second patient.

5. Undiagnosed pregnancy was noted in 10 cases. Eight out of the ten were associated with fibroids. A detailed history, a careful pelvic examination, and longer observation before operation will prevent operation upon this type of patient.

6. Hysterectomies done after the diagnosis of pregnancy for small fibroids or minor complaints can rarely be defended. Departmental controls will correct this situation.

7. Hysterectomy for therapeutic abortion was carried out on 31 patients. The prevention of future pregnancies in patients with serious disease of other systems was a factor in the choice of the procedure.

8. Four hundred seventeen patients with tubal pregnancies were admitted to the hospital. One hundred sixty-eight were diagnosed before rupture. Hysterectomy was carried out on 46 patients, 28 for pathology in the pelvis, 5 because of the second tubal pregnancy, one for multiparity, and 12 without other pathology noted.

9. There were 17 patients with rupture of the uterus in this series. Eight ruptures occurred before the onset of labor. Seven of these 8 patients had had a previous section. In 5 patients rupture followed version or breech delivery, and in 4 patients it resulted from precipitous labors and deliveries.

10. There were 6 deaths in this series of 175 hysterectomies. Three followed full-term pregnancies, and 2 of these patients probably would have survived had fibrinogen been available. Three deaths followed hysterectomies for therapeutic abortion. Two patients were very ill at the time of operation.

### Discussion

DR. C. R. BATES, Wichita Falls, Texas.—Dr. Folger has indicated that the problem of sterilization probably influenced the choice of operative procedure. This was apparently a consideration in 43 per cent of the cesarean section hysterectomies. The question of whether one might best treat his patient by the simple addition of tubal ligation to the already performed cesarean section, or whether the addition of total hysterectomy is the procedure of choice has been the subject of much discussion. That the procedure can be carried out safely, I think, has definitely been shown. The increased number of well-trained physicians practicing the specialty along with the improved pre- and postoperative care have decreased the hazards of the procedure. It is indeed a good procedure in the proper hands.

Of the 18 postpartum patients who underwent hysterectomy, hemorrhage was the primary consideration in 15 cases and played a part in 2 others. Clarification of the problem of postpartum hemorrhage and the increasing availability of fibrinogen, blood, and blood substitutes has greatly reduced the necessity for hysterectomy. Two of the 6 deaths reported in this series occurred in this group. It is quite possible, as the author states, that with our present-day armamentarium these deaths might well have been avoided.

I think the author's classification might be clarified somewhat by the deletion of the groups "hysterectomy near viability" and "pregnancy incidental to other pathology," and by placing the patients so classified in their respective groups of therapeutic abortion and ectopic pregnancy.

Ten of the cases reviewed showed pregnancy as a pathologic diagnosis. We are all guilty of errors in diagnosis and treatment of our patients on occasion. However, such an error as this may be catastrophic. This certainly reminds us of the necessity for a careful history and physical examination before any surgical procedure is undertaken. Never can we forget that complications of pregnancy account for the greatest number of cases of abnormal vaginal bleeding in the childbearing age.

The author states that the group of patients who were operated upon with a known pregnancy was the hardest to interpret. I must agree that evaluation of these cases is indeed difficult, for the preoperative diagnosis hardly justifies termination of a pregnancy. I wholeheartedly agree that there must be sufficient and considerable pathology present to

justify the hysterectomy in the presence of a known pregnancy. It is, indeed, a rare fibroid that justifies termination of a pregnancy. By the same token, the desires of the patient do not necessarily justify the operation.

Certainly, the indications for therapeutic abortion have changed during the period covered by the survey. As progress continues in medicine the indications will be further decreased. This procedure as a means of interruption of pregnancy and sterilization is, to me, the procedure of choice. I am sure many of you have been faced with the problem of a woman who has had a therapeutic abortion and is again pregnant. If hysterectomy had been done as the original procedure that problem would not exist.

It was interesting to me to note that 7 of the 8 patients who suffered a ruptured uterus had had a previous section. Six of these had a repair of the rupture done; one had had a previous rupture. I would like to ask Dr. Folger if he can tell us the outcome of this group and why, since a repair was done, they were included in this group. I am reluctant to attempt the repair of a uterine rupture and allow another pregnancy.

DR. CHARLES E. GALLOWAY, Evanston, Ill.—I wish to ask Dr. Folger if he did any tubal ligations for sterilization following cesarean sections, as well as these 75 hysterectomies.

As I reported to the Academy meeting last September, out of 400 consecutive hysterectomies, I had only 2 cesarean hysterectomies. One was immediately post partum. During that same period of time, on cesarean section patients, I did 52 tubal ligations. In other words, there was a ratio of 52 ligations to 2 hysterectomies.

Also, we have here 12 hysterectomies at the time of ectopic pregnancy. There is an axiom of surgery that I do not think anybody can deny, and that is that the more operating you do, the more complications and deaths you are going to have. You cannot escape that. It does not make any difference how skillful you are.

If you can do a minor procedure and effect sterilization, you have no business subjecting the patient to an increased risk to accomplish the thing. That is just morally not right.

I realize that this is a controversial issue, and there are plenty of hospitals in this country that do not permit us to do tubal ligation, even in connection with cesarean section, but the price of freedom is eternal vigilance, and it is up to us physicians to see to it that we are not pushed around, because we know, every one of us, that taking out a uterus right after a baby is out of it is at least ten times as risky as ligation of the tubes after the baby has been removed.

DR. IRVING F. STEIN, Chicago, Ill.—I wish to ask one question about the type of cesarean sections which were followed by rupture. Were they classical, low cervical, with longitudinal incision, or transverse?

In my experience of over 40 years, I have never seen a rupture of the lower uterine segment with the longitudinal incision.

DR. FOLGER (Closing).—I did not want to create the impression that I am advocating this surgery that was done on these patients for sterilization. I only brought out the point that, in going over these charts, we tried to be as fair as we could to the operators and the patients, and I thought perhaps at least we ought to put these facts down.

We work in a hospital where, of course, sterilization is not prohibited. I would say we do almost routine tubal ligations after cesarean section, unless there is serious pathology, and most of these patients had serious pathological conditions following section.

I think Dr. Bates asked why I included the ruptures that were repaired. That was just to close out the group of cases I did not include, the ones that had hysterectomies.

As to Dr. Galloway's remarks about hysterectomy done at the time of operating for ectopic pregnancies, I have absolutely no quarrel there at all.

Concerning Dr. Stein's question about the type of section—to my knowledge, they all had the midline incision. I am not sure that I could say they were all classical or low classical. In contrast, I do not recall any of the low transverse group that had ruptures.



## ABO INCOMPATIBILITY IN THE ETIOLOGY OF HEMOLYTIC DISEASE OF THE NEWBORN\*

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SINCE 1941, it has become evident that erythroblastosis may result from isoimmunization induced by antigens other than Rh.<sup>1, 3</sup> Ottenberg,<sup>2</sup> in 1923, suggested the possibility of interaction of the A and B agglutinogens between mother and fetus with resultant pathologic processes. Polayes,<sup>4</sup> in 1928, concluded from the study of cord, fetal, and maternal blood in one thousand cases that an interchange of antigens and antibodies probably does occur between mother and fetus through the placenta. He concluded that by some "protective mechanism" pathologic effects are prevented. In further reviewing the history of this phenomenon, Boorman, Dodd, and Mollison,<sup>5</sup> in 1945, supported the idea that anti-A and anti-B agglutinins may occasionally cause a destruction of fetal erythrocytes of Group A or Group B, respectively. This was felt to be one of the etiological factors in some cases of erythroblastosis fetalis. Halbrecht<sup>6</sup> reviewed ten thousand births and described 60 patients with a clinical picture he designated "icterus praecox." Fifty-seven of these infants had blood incompatible with that of the mother so that the serum of the mother agglutinated the red cells of the child. Frequently, the diagnosis was made on inadequate criteria and for this reason ABO hemolytic disease was disregarded for some years. An important adjunct toward the final proof of the existence of ABO incompatibility was provided by the "Erythrocyte Survival Studies."<sup>7, 10</sup> In these studies, transfused Group O blood survived normally in affected infants while red cells, incompatible with the mothers' serum, disappeared rapidly.

### Mechanism of ABO Incompatibility

The mechanism of ABO incompatibility as a cause of hemolytic disease is similar to that which occurs in Rh isoimmunization. In a mother with Group O, Rh-positive blood and an offspring with Group A blood, the antigen of the fetus inherited from the father would enter the mother's circulation by the placenta. Presumably, the A antigen of the fetus would induce in the mother an increase in the titer of anti-A agglutinin. The transfer of this anti-A agglutinin across the placental barrier occurs as an anti-Rh agglutinin is transported across the placental barrier.<sup>8</sup> There is some question whether a placental defect is necessary to effect this transfer of material.<sup>9</sup> The proposed mechanism of transfer is illustrated in Fig. 1.

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### Compatible and Incompatible Mating

Discussion of the blood group types necessary for isoimmunization in ABO incompatibility leads to a consideration of compatible matings and hetero-specific pregnancies. A compatible mating is defined as one in which the parents belong to the same blood groups or one in which the dominant factor A or B is present in the mother's blood. In an incompatible mating, the dominant factor A or B or both are present in the father but lacking in the mother.<sup>11</sup> In the white population of the United States and Europe, 65 per cent of all matings are compatible, and 35 per cent incompatible. Since most individuals of blood group A or B are heterozygotes (AO and BO rather than AA and BB), incompatibility of the red cells with the mother's serum occurs in only 26 per cent of all births (Table I).

TABLE I. INCOMPATIBLE MATINGS OF ABO SYSTEM. DOMINANT FACTOR A OR B OR BOTH ARE PRESENT IN THE FATHER BUT LACKING IN THE MOTHER

BLOOD GROUP OF FATHER	BLOOD GROUP OF MOTHER
A	O
A	B
B	O
B	A
AB	B
AB	O
AB	A

### Heterospecific Pregnancy

Heterospecific pregnancy refers to a pregnancy where a child is shown to have a blood group different from that of the mother. Homospecific pregnancy is one where the blood groups of mother and child are the same. Thus, in a heterospecific pregnancy the child exhibits a blood group antigen of the ABO system which is absent from the maternal red blood cells.<sup>11</sup> This occurs in 20 per cent of pregnancies and in all such cases the mother's serum must contain an isoagglutinin which can react with the child's cells (Table II).

TABLE II. HETEROSPECIFIC PREGNANCY SHOWING INFANT BLOOD GROUP DIFFERENT FROM THAT OF THE MOTHER

BLOOD GROUP OF MOTHER	BLOOD GROUP OF CHILD
O	A,B
A	AB,B
B	AB,A
AB	No heterospecificity

It is supposed that where incompatibility is present isoimmunization of the mother takes place by the abnormal passage either of fetal erythrocytes or of soluble group-specific substances present in the fetal tissue fluids through the placenta into the maternal circulation.<sup>6, 12-14</sup>

### Material

The records of the obstetrical and newborn services of the Ohio State University Hospital and Children's Hospital were reviewed for a period of

two and one-half years. The incidence of ABO and Rh incompatibility was compared. Clinical considerations, differential diagnosis, management, and results of treatment are discussed.

### Observations

*Incidence.*—From June 1, 1953, to Jan. 1, 1956, there was a total of 8,914 live births. During this same period, we encountered 26 cases of ABO incompatibility (0.291 per cent) and 55 cases of Rh incompatibility (0.618 per cent) (Table III).

TABLE III. INCIDENCE OF ERYTHROBLASTOSIS FETALIS AT OHIO STATE UNIVERSITY HEALTH CENTER, JUNE, 1953, TO JANUARY, 1956

	NUMBER	PER CENT
Live births	8,914	100.0
ABO	26	0.291
Rh	55	0.618

The frequency of hemolytic disease as a result of ABO incompatibility varies from 5 to 20 per cent of all cases of hemolytic disease of the newborn.<sup>9, 11, 15, 16</sup> Since definite criteria of diagnosis have been inadequate, however, the true frequency is still to be determined by a systematic study. As

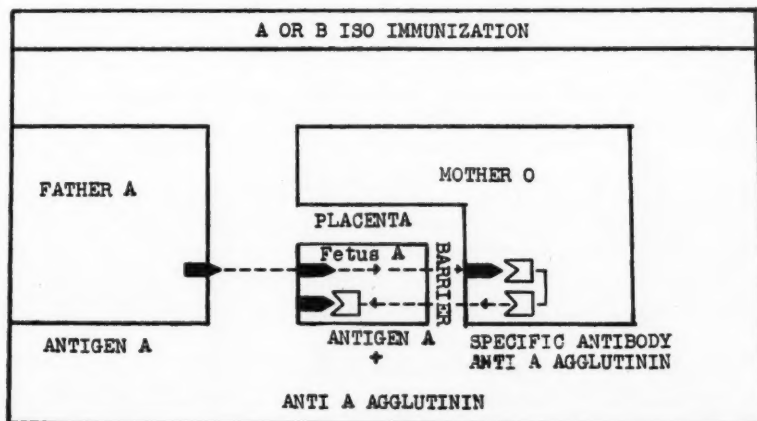


Fig. 1.—Mechanism of ABO incompatibility as a cause of hemolytic disease. (After Polayes.<sup>8</sup>)

was anticipated, there was a progressive increase in the number of new cases diagnosed as interest was renewed in this problem. In the white race, as clinicians become more aware of ABO incompatibility and more discerning laboratory tests are developed, the incidence of this specific isoimmunization will possibly be numerically equal to that found due to Rh sensitization.

*Maternal and Fetal Typing.*—We have already defined compatible and incompatible matings, as well as heterospecific and homospecific pregnancies. The maternal type was found to be predominantly O, Rh positive. The fetal blood type was more evenly distributed, being A, Rh positive in almost 69 per cent of our fetal typings. The remaining 31 per cent of our fetal types were B, Rh positive (Table IV). As noted by others, this is the usual maternal and fetal serologic picture in isoimmunized infants.<sup>6, 9</sup>

TABLE IV. BLOOD TYPES ENCOUNTERED

TYPE	MATERNAL		FETAL	
	NO.	PER CENT	NO.	PER CENT
O, Rh positive	23	88	0	0
O, Rh negative	3	12	0	0
A, Rh positive	0	0	18	69
B, Rh positive	0	0	8	31
Total	26	100	26	100

*Maternal Anti-A or Anti-B.*—In establishing the diagnosis of a hemolytic response on the basis of ABO incompatibility, several criteria must be satisfied. Maternal and fetal typing must be such that isoimmunization can occur. We tried to establish the diagnosis further with maternal anti-A and anti-B titers as well as available Coombs testing. Rh incompatibility was ruled out on the basis of maternal and fetal typing, but the latter two laboratory tests were used to distinguish ABO incompatibility from physiologic jaundice of the newborn. Table V shows the incidence and titer of maternal anti-A or anti-B.

TABLE V. MATERNAL ANTI-A OR ANTI-B

TITER	NUMBER	PER CENT
Not drawn	1	3.9
Negative	3	11.5
1-320	1	3.9
1-640	6	23.1
1-1,280	3	11.5
1-2,560	7	26.9
1-5,120	4	15.3
1-20,480	1	3.9
Total	26	100.0

*Direct Antiglobulin Testing.*—As others<sup>11</sup> have consistently reported, and we have substantiated in this report, Coombs tests in hemolytic disease due to ABO incompatibility were predominantly weakly positive or negative (Table VI). This is in contradistinction to isoimmunization on the basis of Rh incompatibility where 2 and 3 plus Coombs tests portend severe hemolytic disease.

TABLE VI. RESULTS OF DIRECT ANTIGLOBULIN TESTING OF CORD BLOOD

COOMBS	NUMBER	PER CENT
Negative	5	19.2
1 plus	17	65.4
2 plus	1	3.9
3-4 plus	0	0.0
Unknown	3	11.5
Total	26	100.0

*Correlation of Maternal Titer, Coombs Test, and Infant Bilirubin Level.*—Accumulated data show an interesting comparison of the maternal titer, Coombs test, and infant bilirubin level. As expected, there is no correlation between elevated maternal titers of anti-A or B and a more strongly positive infant Coombs test. Furthermore, infants of mothers with high maternal titers did not necessarily have the highest serum bilirubin levels. We, therefore, feel that the height of maternal titer and degree of positive Coombs test offer no help in prognosticating the severity of the neonatal hemolytic reaction. As expected, the infants who developed higher serum bilirubin levels within six to twenty-four hours required exchange transfusion (Table VII).



TABLE VII. CORRELATION OF MANAGEMENT WITH MATERNAL ANTIBODY TITER, COOMBS TEST, AND SERUM BILIRUBIN

MATERNAL TITER	COOMBS TEST	BILIRUBIN (MG. %)	EXCHANGE TRANSFUSION
Negative	1 plus	23.3	0
Negative	1 plus	17.6	1
Negative	Unknown	19.9	2
1-320	1 plus	23.3	0
1-640	1 plus	16.0	1
1-640	Negative	17.6	1
1-640	1 plus	19.9	2
1-640	1 plus	30.0	0
1-640	Negative	25.7	2
1-640	Negative	28.0	0
1-1,280	1 plus	20.8	0
1-1,280	1 plus	15.5	0
1-1,280	1 plus	10.3	0
1-2,560	?	ND	0
1-2,560	1 plus	20.2	0
1-2,560	1 plus	17.5	1
1-2,560	2 plus	13.6	1
1-2,560	1 plus	21.1	1
1-2,560	1 plus	16.0	1
1-2,560	Negative	18.6	1
1-5,120	?	ND	0
1-5,120	1 plus	19.6	0
1-5,120	1 plus	23.6	0
1-5,120	1 plus	17.0	0
1-20,480	Negative	20.5	1

It is interesting to note the average peak level of bilirubin recorded in our series. This is misleading since our 26 reported cases represent only those cases of ABO incompatibility that were unequivocally proved by clinical and laboratory evaluation. There were instances of ABO hemolytic disease less severe in nature which were inadequately worked up serologically. These are not included in our data. Therefore, our reported incidence of ABO incompatibility is undoubtedly low and, conversely, our reported average peak serum bilirubin level is inordinately high. It is clear from our data that the onset of jaundice due to ABO incompatibility is much earlier than it is in physiologic disease of the newborn.

*Appearance of Jaundice.*—The early onset of jaundice was one of the most significant clinical findings. In the severe cases, jaundice (Table VIII) appeared soon after birth (in 25 of 26 cases in less than twenty-four hours). The icterus increased in intensity and in some cases was as pronounced as that seen in infants with Rh disease.

TABLE VIII. ONSET OF JAUNDICE

APPEARANCE (HOURS)	NO.
6-12	15
12-24	10
24-48	1
Total	26

Peak bilirubin average, 19.25 mg. %

There may be varied degrees of anemia, reticulocytosis, and normoblastemia. In contrast to the almost uniform macrocytosis encountered in Rh disease, ABO incompatibility is characterized by moderate-to-pronounced microspherocytosis with the expected increase in osmotic and mechanical fragility of the red cells.<sup>17, 18</sup>

### Results of Treatment

During the period of this study, 20 of the 26 affected infants were transferred to Children's Hospital for further treatment and observation. Of the 6 infants observed at University Hospital, none received transfusions. The peak bilirubin levels remained below 20 mg. per cent, and with jaundice subsiding, they were discharged home with their mothers.

Of 20 infants transferred, 8 were observed without active treatment. Two received simple transfusions with O Rh-negative blood. Seven received one exchange transfusion and 3 had two exchange transfusions. In this group of infants, no kernicterus was encountered, but one infant under 2,500 grams died of aspiration pneumonia. The group of 19 surviving infants were discharged improved and required no further treatment (Table IX).

Table IX also shows final results in 29 other infants admitted to Children's Hospital from other hospitals in the Columbus area. Two infants died, and both had evidence of kernicterus. Of probable clinical significance is the fact that both infants were premature, and both were admitted to the hospital at 72 hours of age. Early recognition is important and may be difficult, especially in prematures, as development of kernicterus is more likely in this group.

TABLE IX. RESULTS OF TREATMENT

	OHIO STATE UNIVERSITY	CHILDREN'S HOSPITAL	OTHER HOSPITALS
Observed	6	8	21
O Rh-negative transfusion	0	2	0
Exchange transfusion (once)	0	7	5
Exchange transfusion (twice)	0	3	3
Living	6	19	27
Kernicterus	0	0	2
Died	0	1*	2†

\*Premature, aspiration pneumonia.

†Premature, admitted after 72 hours of jaundice.

Observation was necessary in 54 per cent of cases studied. Hemolytic disease due to ABO incompatibility was less severe than that associated with Rh disease. Indications for exchange transfusion were the same as those used for Rh hemolytic disease. There was some reluctance to give exchange transfusions to the infant with ABO incompatibility because of the feeling that the hemolytic response was usually less severe than in the Rh-sensitized child. The morbidity and mortality are the same for exchange transfusions in both ABO- and Rh-incompatible infants, except that the latter are more often critically ill. There were no deaths attributed to transfusions in this group. The response to treatment is favorable and prognosis good in infants with early diagnosis of ABO disease.

### Discussion

The familiar clinical manifestations seen in Rh-Hr hemolytic disease may be present in ABO hemolytic disease. The picture may vary from a stillborn hydropic infant to one who appears clinically well and in whom hemolytic disease is diagnosed with considerable difficulty. It has also been suggested as a possible cause of abortion and toxemia.<sup>6, 19, 20, 21</sup> Particularly in prematurity, the diagnosis cannot be made with certainty and the condition may be indistinguishable from physiologic jaundice. In the latter condition, the onset of

jaundice is usually on the second or third day when the icterus of ABO incompatibility is at its peak. A serum bilirubin of 10 mg. or higher in a newborn at term during the first twenty-four hours is considered diagnostic of hemolytic disease.

The diagnosis of ABO hemolytic disease is somewhat more complicated than that of Rh incompatibility. The occurrence of ABO hemolytic disease in pregnancy cannot be predicted, even in a mother who previously gave birth to an infant with this disorder.<sup>22, 23</sup> According to Zuelzer,<sup>9</sup> a minority of cases of heterospecific pregnancy in the postpartum period exhibit a specific immune response to fetal blood-group antigens. This antibody response was found only in heterospecific pregnancies of mothers with infants who secrete A-B substances, and in the case of group A infants, only if the infant belonged to subgroup A<sub>1</sub>. The response may subside, but is reported to be present as late as seven months after delivery. Thus far, there is no evidence that the postpartum responses of heterospecific pregnancy produce a cumulative effect on the serum in subsequent pregnancies in a manner comparable to Rh sensitization. The obstetrician is never aware of trouble prior to birth of the baby.

Diagnosis is further complicated by the fact that the first-born is affected in about 50 per cent of all cases in contrast to Rh sensitization, which is extremely rare in a first pregnancy. Interpretation of titration values for anti-A and anti-B in maternal serum is difficult. High titers in saline are not significant in themselves since they can occur without affecting the infant. However, the rise in titer may be more marked in those women whose infants are of incompatible blood groups, especially when the infant is a secretor of A-B substances.<sup>12, 13</sup>

Mothers of affected infants usually have incomplete anti-A and anti-B antibodies as demonstrable with compatible serum, plasma, or positive indirect antiglobulin methods. The value of this is demonstrated by the fact that (1) anti-A and anti-B occur as normal antibodies and (2) immune anti-A or B has not the same diagnostic importance as the occurrence of anti-Rh, which always signifies potentially dangerous sensitization.

Finally, a positive result of a direct antiglobulin test on infant red cells establishes the diagnosis with certainty in Rh disease, whereas in ABO disease the red cells may reveal a negative or a weakly positive Coombs test.

Fortunately, in most of the infants with hemolytic disease due to ABO incompatibility, the disease is mild and requires no treatment. When it is moderately severe, a simple transfusion with packed O red cells is usually all that is necessary. Severely affected infants should be treated by exchange transfusion. Premature infants are prone to develop kernicterus more readily than term infants and should also have the benefit of exchange transfusion. Indications for exchange transfusion are not as clear-cut as in Rh hemolytic disease, but each case and the hemolytic process is evaluated on an individual basis. Bilirubin over 20 mg. per cent, an increase of serum bilirubin of 0.5 to 1.0 mg. per hour, or reticulocytosis over 20 per cent are considered adequate indications for exchange transfusion.

### Summary

1. Fifty-five cases are reported of hemolytic disease of the newborn due to ABO incompatibility. Twenty-six cases from Ohio State University Hospital are reported in detail.
2. The etiology and mechanism of ABO incompatibility are discussed.
3. Compatible and incompatible matings are defined, and the relationship to homospecific and heterospecific pregnancies is discussed.
4. The incidence and recognition are compared with Rh sensitization in 8,914 live births over a period of two and one-half years.
5. Maternal anti-A and anti-B substances are correlated with fetal serum bilirubin, Coombs test, and the need for exchange transfusion.
6. The clinical manifestations of ABO disease are correlated with those of Rh-Hr incompatibility. The complications of differential diagnosis and difficulty in predicting ABO disease are presented.
7. Management, results of treatment, and indications for exchange transfusion are discussed.

We gratefully acknowledge the advice, assistance, and use of materials from Dr. Warren Wheeler and Dr. Thomas Shaffer of the Department of Pediatrics and Children's Hospital.

### References

1. Levine, P., and Polayes, S. H.: *Ann. Int. Med.* 14: 1903, 1941.
2. Ottenberg, R.: *J. A. M. A.* 81: 295, 1923.
3. Levine, P.: *Arch. Path.* 37: 83, 1944.
4. Polayes, S. H., Lederer, M., and Wiener, A. S.: *J. Immunol.* 17: 545, 1929.
5. Boorman, K. E., Dodd, B. E., and Mollison, P. L.: *J. Path. & Bact.* 57: 157, 1945.
6. Halbrecht, I.: *Am. J. Dis. Child.* 68: 248, 1944.
7. Zuelzer, W. W., and Kaplan, E.: *Am. J. Dis. Child.* 88: 307, 1954.
8. Polayes, S. H.: *Am. J. Dis. Child.* 69: 99, 1945.
9. Zuelzer, W. W., and Kaplan, E.: *Am. J. Dis. Child.* 88: 158, 1954.
10. Kaplan, E., and Zuelzer, W. W.: *J. Lab. & Clin. Med.* 36: 511, 1950.
11. Davidsohn, I.: *Obst. & Gynec.* 8: 318, 1956.
12. Smith, G. H.: *J. Path. & Bact.* 57: 113, 1945.
13. Jakobowicz, R., and Bryce, L. M.: *M. J. Australia* 1: 669, 1948.
14. Mollison, P. L.: *Blood Transfusion in Clinical Medicine*, Oxford, England, 1951, Basil Blackwell & Mott, Ltd.
15. Clifford, S. H., and Hertig, A.: *New England J. Med.* 33: 317, 1937.
16. Hellman, L. M., and Hertig, A.: *AM. J. OBST. & GYNEC.* 36: 137, 1938.
17. Robinson, G. C., Phillips, R. M., and Prystowsky, M.: *Pediatrics* 7: 164, 1951.
18. Damashek, W., and Schwartz, S. O.: *Am. J. M. Sc.* 196: 769, 1938.
19. Sora, P.: *Minerva ginec.* 6: 80, 1954.
20. Levine, P.: In *National Committee on Maternal Health, Inc.: The Abortion Problem*, Baltimore, 1944, Williams & Wilkins Company.
21. Chown, B., and Lewis, M.: *Canad. M. A. J.* 58: 504, 1948.
22. Witebsky, E.: *Blood, Special Issue No. 2*: 66, 1948.
23. Levine, P.: *Tr. New York Acad. Sc.* 13: 205, 1951.

### Discussion

DR. A. R. PRUIT, Roswell, N. M.—Here is a disease which should account for 5 to 20 per cent plus of all erythroblastosis yet I am sure that at the present time most of us are recognizing nowhere near that figure. Certainly we are not seeing the cases in the hospitals with which I am associated.

From the clinical standpoint the problem resolves itself into (1) early recognition of the presence of jaundice in the baby; (2) prompt measures to determine the diagnosis and severity of the disease; and (3) transfusion or replacement transfusion where indicated.



Since there is no practical way to be forewarned by prenatal antibody checks, one must depend on early recognition of developing jaundice. This can be done not only through increased awareness of the possibility by the obstetrician and pediatrician but also by repeated warning and instruction to the nursing staff to report immediately any suggestion of jaundice in an infant, especially in the first thirty-six hours of life. I wonder how many of the milder cases we are missing because of the masking effect of artificial light in the nurseries.

It should be emphasized that jaundice which develops in the first twenty-four hours or at any time with a serum bilirubin level of 10 mg. or more should be considered pathological. Differential diagnosis should be done, as Dr. Copeland stated, by the Coombs test and Rh and ABO typing. If there is no Rh incompatibility and it is determined to be ABO heterospecificity, then the outlined procedures to determine incompatibility should be done. In this regard I would like to ask Dr. Copeland for his comment on the value and practicality of the so-called double Coombs test and the Witebsky differential test in determining the presence of ABO disease.

In a forthcoming publication of a paper presented by Potter before the May meeting of the Chicago Gynecological Society, another cause of jaundice in the newborn will be emphasized. The name of this disease, as I recall, was cytomegalic inclusion body disease of the newborn. This disease closely approximates erythroblastotic disease but no incompatibility of blood can be found. Smith has identified the causal agent as a virus not infrequently found in the salivary glands of the mother. Evidently the virus crosses the placental barrier and produces liver and kidney damage. As the disease process involves the kidney this disease can be differentiated from erythroblastosis by examination of the urine of the newborn. Centrifugation of the urine and examination of the sediment will show very large cells with tremendously large nuclei which cells will not be found in the urine of infants with erythroblastosis.

As for the treatment of erythroblastosis due to ABO incompatibility, I wonder if Dr. Copeland would agree to the statement that any premature infant, that is, any infant below 38 weeks' gestation with a serum bilirubin of 10 mg. or above, and any term infant with a serum bilirubin of 20 mg. or above, regardless of clinical appearance, should have exchange transfusion. I would also like his comment on the use of Type O blood for exchange transfusion, whether this blood should be compatible with the mother's serum as well as with the infant's, and whether Witebsky substance is invariably added.

DR. COPELAND (Closing).—We have had no personal experience with the use of the Coombs or Witebsky test, although, according to Zuelzer and Kaplan and, I believe, Davidsohn's recent article, this should also be of tremendous value in diagnosing ABO incompatibility.

Talking with the pediatricians about how they decide which babies should have exchange transfusions, I cannot get any uniformity of opinion. There are certain instances in which they can demonstrate better than 10 mg. of bilirubin in prematures and as much as 20 to 22 mg. of bilirubin in term-sized infants, and they will give blood to one set and the others they will observe.

Many cases of so-called physiologic jaundice are actually ABO incompatibility, and in the milder forms or moderately severe forms in which jaundice develops there may be some evidence of cerebral damage due to the high bilirubin levels. Perhaps some mental deficiency may result in some children from this high bilirubinemia, that we could possibly prevent by giving transfusions.

## SARCOMA AND SARCOMA-LIKE PROLIFERATIONS OF THE ENDOMETRIAL STROMA

### III. Stromal Hyperplasia and Stromatosis (Stromal Endometriosis)\*

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THIS report is an outgrowth of an investigation of 56 uterine neoplasms previously classified as sarcomas of the endometrial stroma. The system of classification evolved and our clinical experience with the various types of sarcomas considered to have their origin in the endometrial stroma have been reported elsewhere.<sup>23, 24</sup> In the course of these studies it became apparent that 16 tumors of questionable malignancy had been classified, perhaps erroneously, as sarcomas (Table I). These were 29 per cent of our declared stromal sarcomas, and the serious prognostic connotation of the term "sarcoma" makes it imperative that such gross error be corrected.

That this error is not peculiar to pathologists in our institution has been indicated by Schiffer, Mackles, and Wolfe,<sup>20</sup> who found that of their 49 uterine sarcomas, 20 were actually benign neoplasms. Moreover, Finn<sup>8</sup> noted that in 16 cases in which the diagnosis on the basis of products of dilatation and curettage was sarcoma, 8 of the specimens obtained by hysterectomy contained carcinoma and the remaining 8 were free of evidence of malignant disease. Similarly, that the exact nature of some bizarre stromal lesions is difficult to determine is indicated in the article of Pedowitz, Felmus, and Grayzel,<sup>18</sup> and in that of Schiffer, Mackles, and Wolfe.<sup>20</sup> In these reports, emanating from the same medical center, 3 tumors originally reported as uterine hemangiopericytomas were subsequently reported<sup>20</sup> as examples of stromal endometriosis, inflammatory endometrial polyp, and sarcoma of undetermined type. Also, one of the 5 hemangiopericytomas reported by Greene and Gerbie<sup>11</sup> had been reported previously to be an endometrial sarcoma.

#### Materials and Methods

Available for study were gross specimens representing all 16 of the borderline lesions that have been mentioned, all preserved in 10 per cent commercial formalin (Figs. 1 to 7). These were restudied grossly for evidences of a botryoid configuration, depth of myometrial penetration (especially the

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†The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

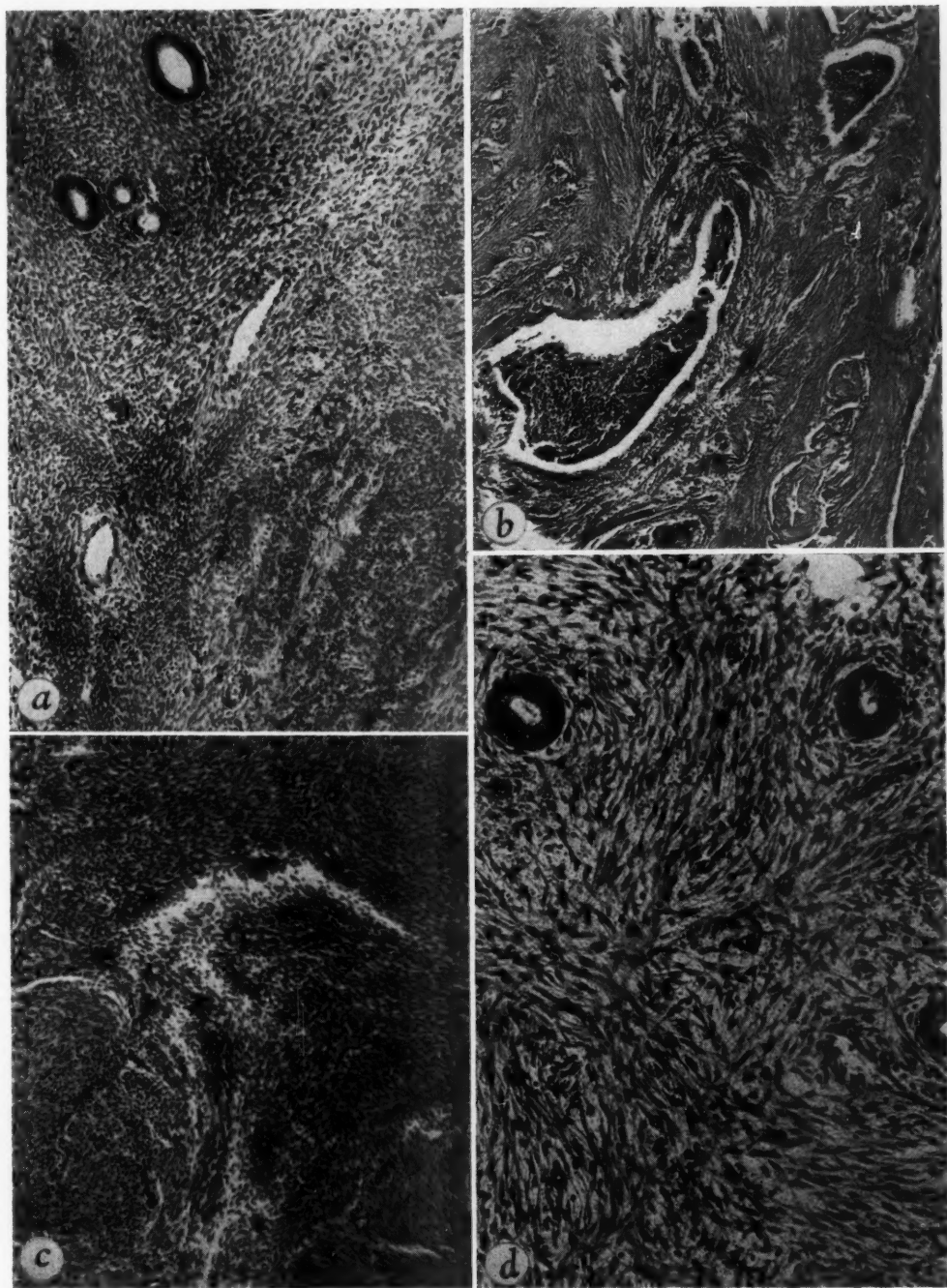


Fig. 1.—*a*, Case 1. Highly cellular endometrial stroma with deep penetration of myometrium and evidence of increased mitotic activity, in both stroma and epithelium. (Hematoxylin and eosin;  $\times 75$ .) *b*, Case 1. Plugs of endometrial stroma without glands, lying deep within the myometrium. Since typical adenomyosis was present in other portions, this may represent stroma where the plane of section missed the epithelial elements. (Hematoxylin and eosin;  $\times 75$ .) *c*, Case 2. Proliferative endometrium with edematous, fibrous stroma. Relative increase in stroma, with stromal and epithelial mitosis. (Hematoxylin and eosin;  $\times 150$ .) *d*, Case 2. Area of stromal-appearing cells deep in myometrium. Typical adenomyosis was present in other portions of specimen. (Hematoxylin and eosin;  $\times 75$ .)

TABLE I. SUMMARY OF CASES

CASE	AGE (YEARS)	PARITY	POST- MENO- PAUSAL	CLASSIFICATION		TREATMENT	RESULTS
				PREVIOUS	REVISED		
1	36	0	No	Fibrosarcoma	Stromal hyperplasia	Total abdominal hysterectomy	Living, no recurrence, 2 years
2	45	0	No	Fibrosarcoma	Stromal hyperplasia	Total abdominal hysterectomy, bilateral salpingo-oophorectomy, postoperative x-ray	Dead after 26 years. Cause unknown
3	46	iii	No	Sarcoma of stroma, Grade 1	Stromal hyperplasia	Total abdominal hysterectomy, bilateral salpingo-oophorectomy	Living, no recurrence, 14 years
4	50	v	No	Sarcoma of stroma, Grade 1	Stromal hyperplasia	Radium, 1,200 mc. hr., total abdominal hysterectomy, bilateral salpingo-oophorectomy	Living, no recurrence, 18 years
5	29	0	No	Sarcoma of stroma, Grade 1	Stromal hyperplasia	Total abdominal hysterectomy, bilateral salpingo-oophorectomy	Living, no recurrence, 4 years
6	39	iii	No	Sarcoma (curettage) Stromatosis (post-operatively)	Stromatosis	Total abdominal hysterectomy, bilateral salpingo-oophorectomy	Living, no recurrence, 5 years
7	44	ii	No	Sarcoma of stroma	Stromatosis	Only subtotal hysterectomy and bilateral salpingo-oophorectomy possible; radium, 600 mc. hr.	Living, no recurrence, 9 years
8	51	0	No	Fibrosarcoma, Grade 1	Stromatosis	Negative curettage, vaginal hysterectomy, abdominal salpingo-oophorectomy	Living, no recurrence, 6 years
9	54	ii	No	Sarcoma of stroma, Grade 1	Stromatosis	Negative curettage, vaginal hysterectomy, abdominal salpingo-oophorectomy	Living, no recurrence, 12 years



10	44	iii	No	Sarcoma of stroma, Grade 1	Stromatosis; slides from elsewhere show same lesion	1951 subtotal abdominal hys- terectomy and 1952 excision of recurrence of tumor in bladder, both elsewhere 3/7/53 removal of cervical stump, left salpingo-oopho- rectomy and excision of in- volved sigmoid 1/30/54 excision of recur- rence in vaginal vault X-ray; radium	Died Oct., 1955, of uremia; pelvic recur- rence. Lived 4 years
11	45	v	No	Sarcoma of stroma	Stromatosis	Negative curettage, vaginal hysterectomy and repair	Living, no recurrence, 1 year
12	74	vii	Yes	Sarcoma of stroma	Stromatosis	Total abdominal hysterectomy, bilateral salpingo-oophorec- tomy, excision of extension fixed to pelvic wall	Living, no recurrence, 9 months
13	51	ii	No	Sarcoma of stroma	Stromatosis	Total abdominal hysterectomy, bilateral salpingo-oophorec- tomy	Living, no recurrence, 6 years
14	39	ii	No	Sarcoma of stroma, Grade 1	Stromatosis	Vaginal hysterectomy, nega- tive curettage	Living, no recurrence, 9 years
15	68	v	Yes	Sarcoma of stroma	Stromatosis	Total abdominal hysterectomy, bilateral salpingo-oophorec- tomy	Died of throat infection after 7 years
16	64	i	Yes	Polypoid sarcoma	Stromatosis	Vaginal hysterectomy (poor surgical risk)	Living, no recurrence, 14 years

rootlike extensions observed in cases of stromal endometriosis), evidences of peritoneal spread, and so forth. Then fresh blocks of tissue were cut and old blocks reassembled. After paraffin blocking, sections were made in a routine manner and stains—hematoxylin and eosin, Masson trichromate, and that for reticulum—were employed serially (Fig. 5, *b* and *c*). As a consequence, it was possible to identify and study individual clusters of cells for appraisal of their reaction to the various ingredients of the stains. Finally, added to the collection of materials were the original slides, many of which were fixed frozen preparations admirably suited for study of nucleoli. In certain instances quick-frozen sections were made to allow "scanning" of the tumor, thus to aid in selection of permanent blocks.

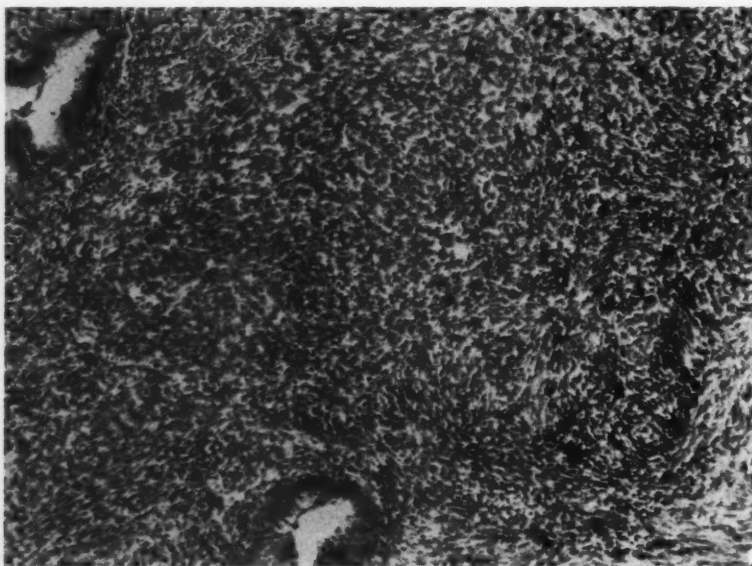


Fig. 2.—Case 5. Scanty endometrial glands with highly cellular, mitotically active stroma; endometritis. (Hematoxylin and eosin;  $\times 150$ .)

In agreement with Schiffer, Mackles, and Wolfe,<sup>20</sup> we considered the four most important histologic criteria for diagnosis of sarcoma to be as follows: (1) increased cellularity, (2) mitosis, (3) giant cells, and (4) pleomorphism. That stromal neoplasms as well as those of myomatous origin may be highly cellular without being malignant needs little emphasis. In contrast, however, to the myogenic sarcomas, where a few mitotic figures may assume diagnostic significance, the occurrence of occasional such figures in the endometrial stroma, or in tumors derived therefrom, is of much less moment. Placing too much reliance on it may lead to an erroneous diagnosis of sarcoma. When stromal mitotic figures are observed concomitantly with evidence of increased mitotic activity in the uterine epithelium, the significance of the former should be minimized and more importance attached to the features of cellularity, pleomorphism, and invasion.

#### Findings

After thorough review of the microscopic sections of the 16 tumors and comparison of them with preparations from a group of 40 in which an unequivocal diagnosis of endometrial sarcoma was acceptable, the following histologic identifications emerged: stromal hyperplasia, 5 cases; stromatosis, 11 cases.



Fig. 3a.—Case 6. Cut surface of gross specimen with myometrial permeation typical of stromatosis.

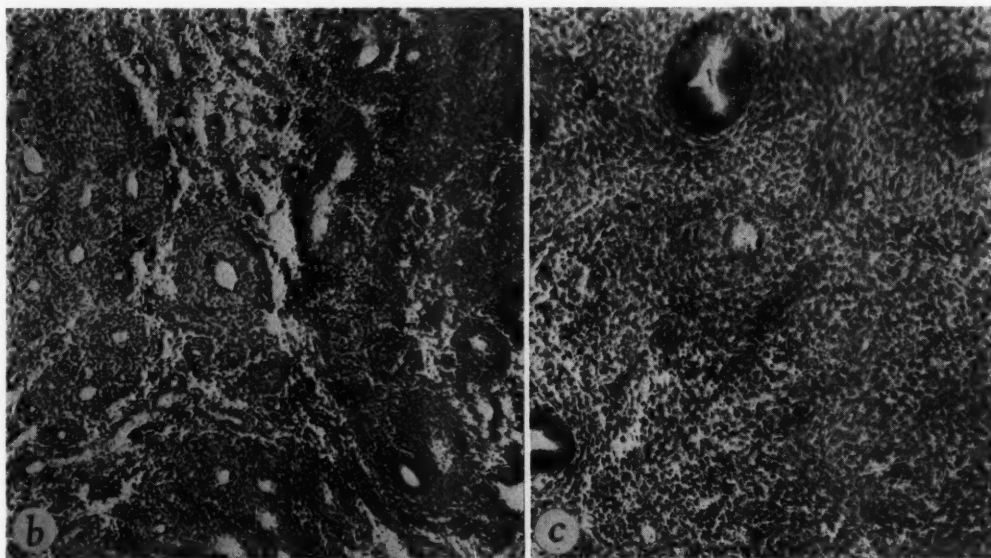


Fig. 3.—*b*, In addition to vascularity, note periglandular (lower right corner) as well as perivascular ("cuffing") distribution of tumor cells. (Hematoxylin and eosin;  $\times 50$ .)  
*c*, Continuity of tumor cells with endometrial stroma and inclusion of glands in tumor substance. (Hematoxylin and eosin;  $\times 100$ .)

*Stromal Hyperplasia.*—At the time of operation, the ages of the 5 patients with stromal hyperplasia ranged from 29 years to 50. All had been actively menstruating. Menorrhagia, metrorrhagia, and other aberrations of menstrual flow had been the presenting symptoms in each case. One patient (Case 5) had noted daily bleeding for 3 months following the passing of a hydatidiform

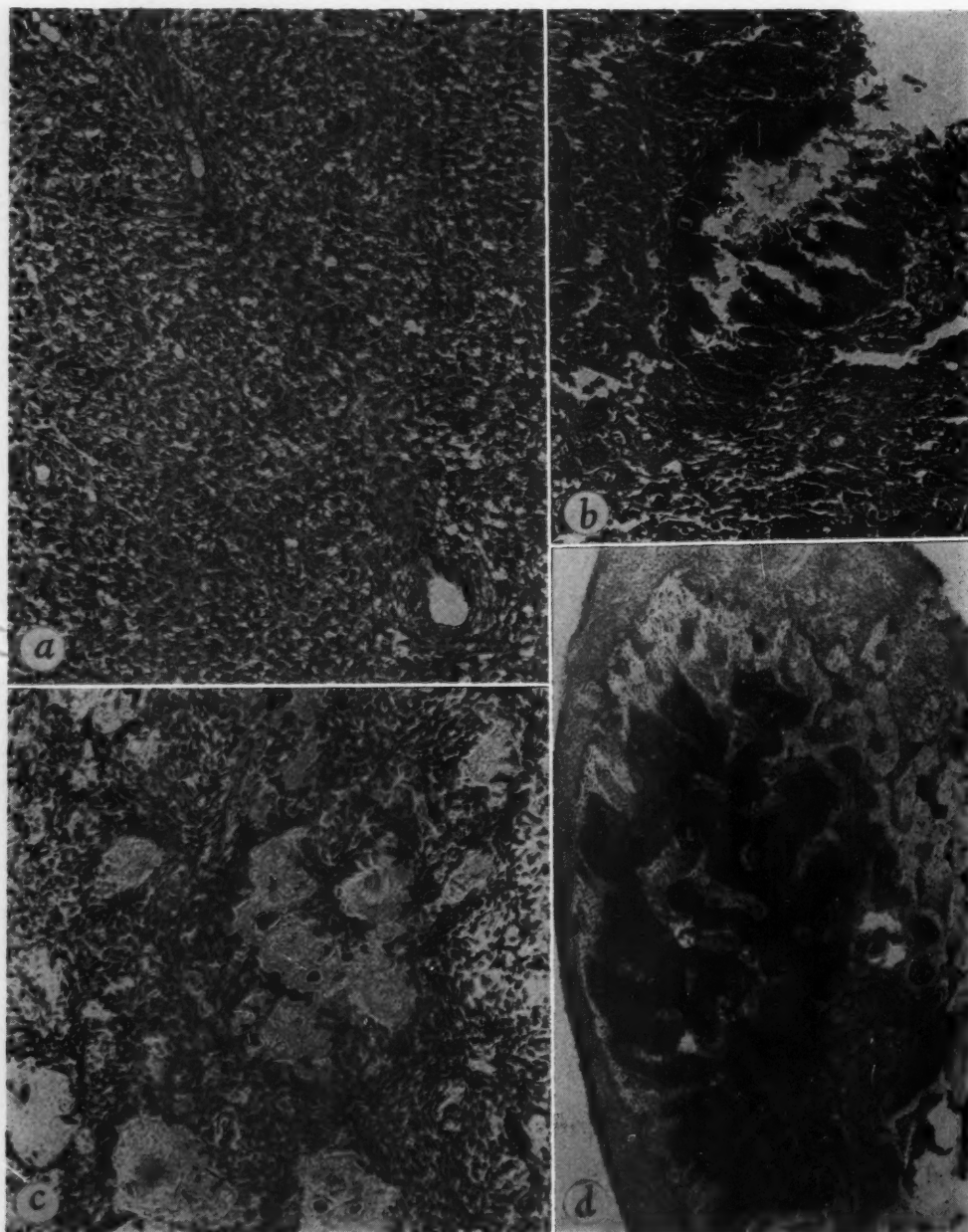


Fig. 4.—Case 8. *a*, Absence of pleomorphism, mitotic activity and perivascular orientation. (Hematoxylin and eosin;  $\times 150$ .) *b*, Tumor replacing endometrium and including a somewhat distorted endometrial gland. (Hematoxylin and eosin;  $\times 125$ .) *c*, Intravascular extension demonstrating metaplasia to osteoid tissue. (Hematoxylin and eosin;  $\times 100$ .) *d*, Cross section of intravascular extension in broad ligament, containing osteoid and osteogenic tissue. (Hematoxylin and eosin;  $\times 30$ .)



mole. Results of biologic assays for chorionic gonadotropin had been negative. In each of the 5 cases, excessive amounts of endometrial tissue had been obtained on diagnostic curettage. Microscopic examination of the tissue had disclosed that proliferation primarily of the endometrial stroma accounted for the abundance of tissue. The endometrium had been in the proliferative phase of the menstrual cycle in 3 cases and in a secretory phase in 2 cases. Apparently the increased mitotic activity, the considerable cellularity, and the overabundance of endometrium had dictated an original diagnosis of sarcoma of the endometrial stroma. Each patient had been subjected to total hysterectomy and 4 of them to additional bilateral salpingo-oophorectomy. In

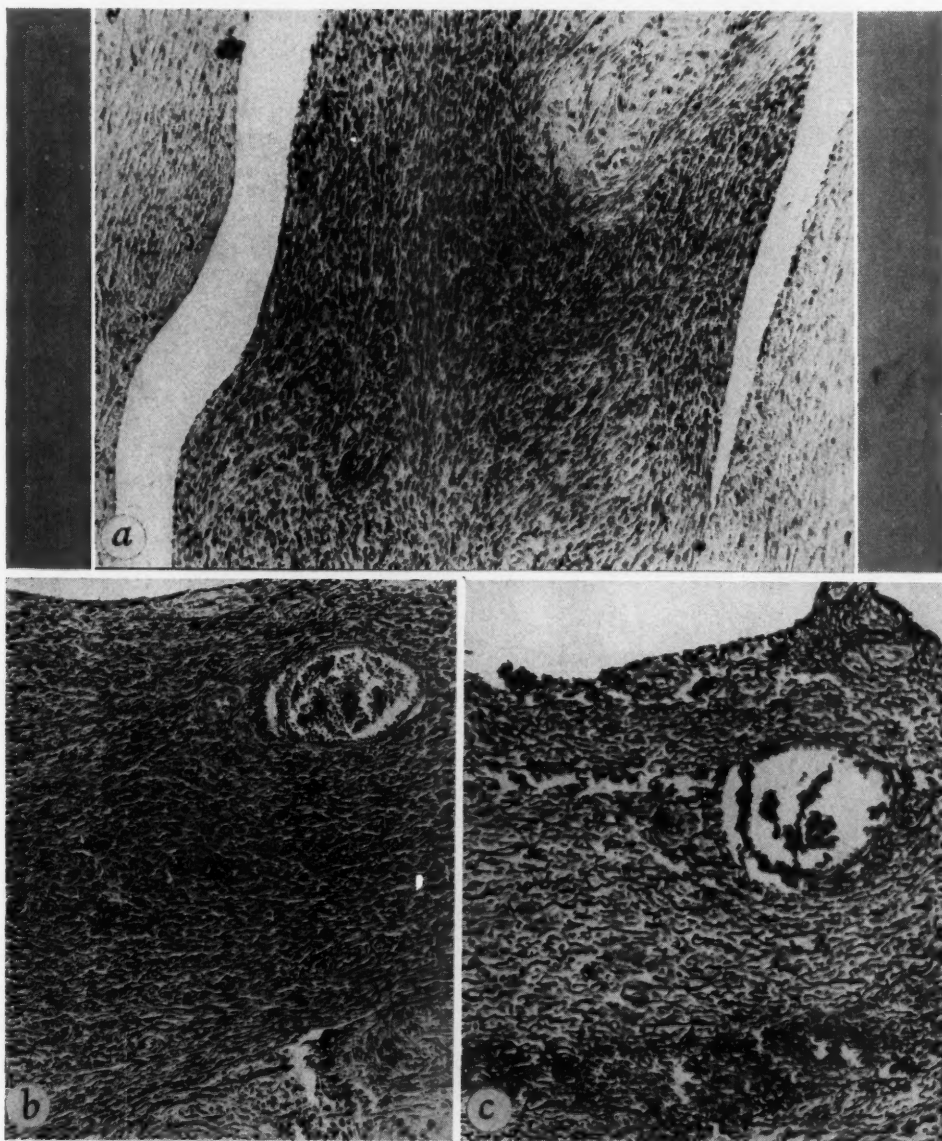


Fig. 5.—Case 11. *a*, Vasoinvasive plug in myometrial extension with stromal cells lacking morphologic variation or mitosis. (Hematoxylin and eosin;  $\times 100$ .) *b* and *c*, Comparative paucity of reticulum without specific pattern in section adjacent to that represented in *a*. (*b*, Masson trichrome,  $\times 100$ ; *c*, reticulum stain,  $\times 175$ .)

Case 4, the patient had received, before operation, 1,200 mc. hr. of radium therapy by intrauterine application; in Case 2, the patient had received x-ray therapy postoperatively.

Following review of the gross specimens, old slides, and additional sections of the preserved endometrium, we believed that there was inadequate justification for the previous diagnosis of sarcoma in these 5 cases. Except for a single polyp of stromal tissue, 2 cm. in diameter (Case 1), gross intrauterine lesions were not noted. External endometriosis (Case 3), adenomyosis

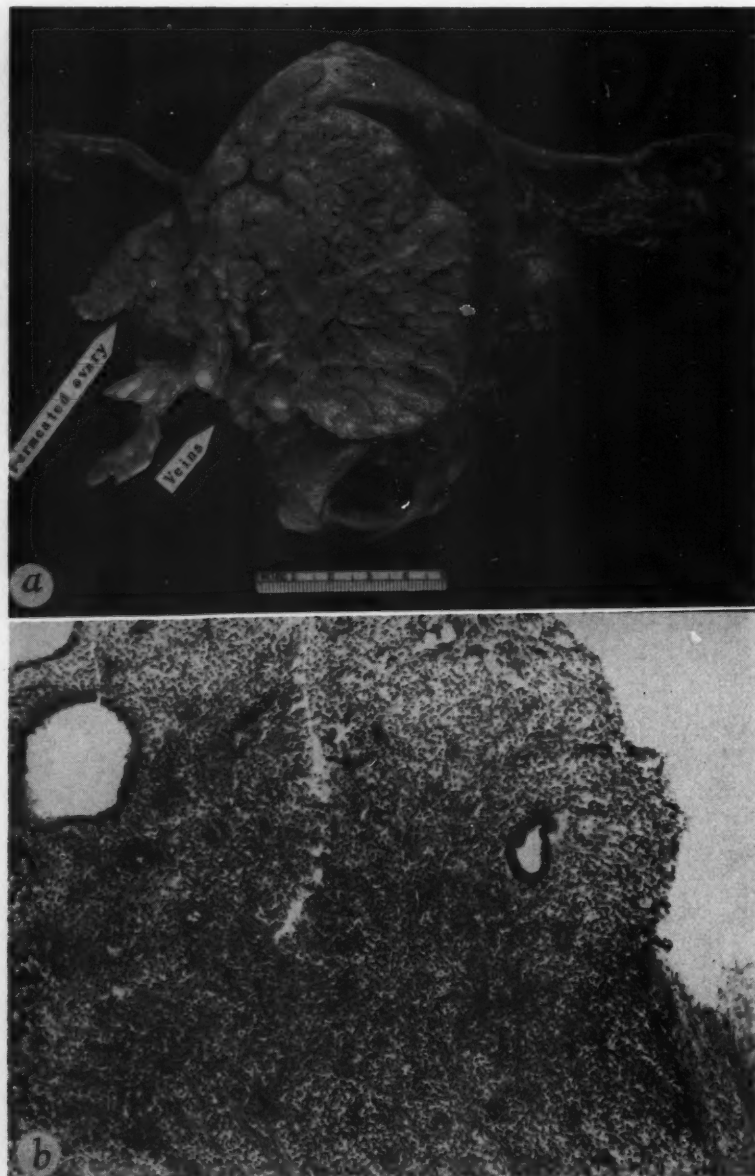


Fig. 6.—Case 12. *a*, Cut surface of yellowish-white, rubbery tumor, measuring 10 by 9 by 7 cm., with extensive permeation of oviduct, ovary, and of veins of right broad ligament even to pelvic wall. *b*, Highly cellular, more hyperchromatic tumor than those represented previously. A few mitotic figures present but little pleomorphism. Note continuity with endometrial stroma and production of glands. (Hematoxylin and eosin;  $\times 75$ .)

(Cases 1 and 2), and leiomyomas (Cases 2 and 4) affected 4 of the 5 patients. Microscopically, 99 per cent of the endometrial tissue consisted of stroma, the contained glands being very sparse though of normal configuration. The stroma, on the other hand, was observed to be highly cellular (Figs. 1, *a* and *d*, and 2) and compact (Figs. 1, *a*, and 2). Although there was evidence of more mitotic activity than appeared to have been physiologic, mitotic figures also were observed frequently in the glandular epithelium. There was no disparity in size of cells or nuclei, nor any hyperchromasia. In Cases 2, 3,

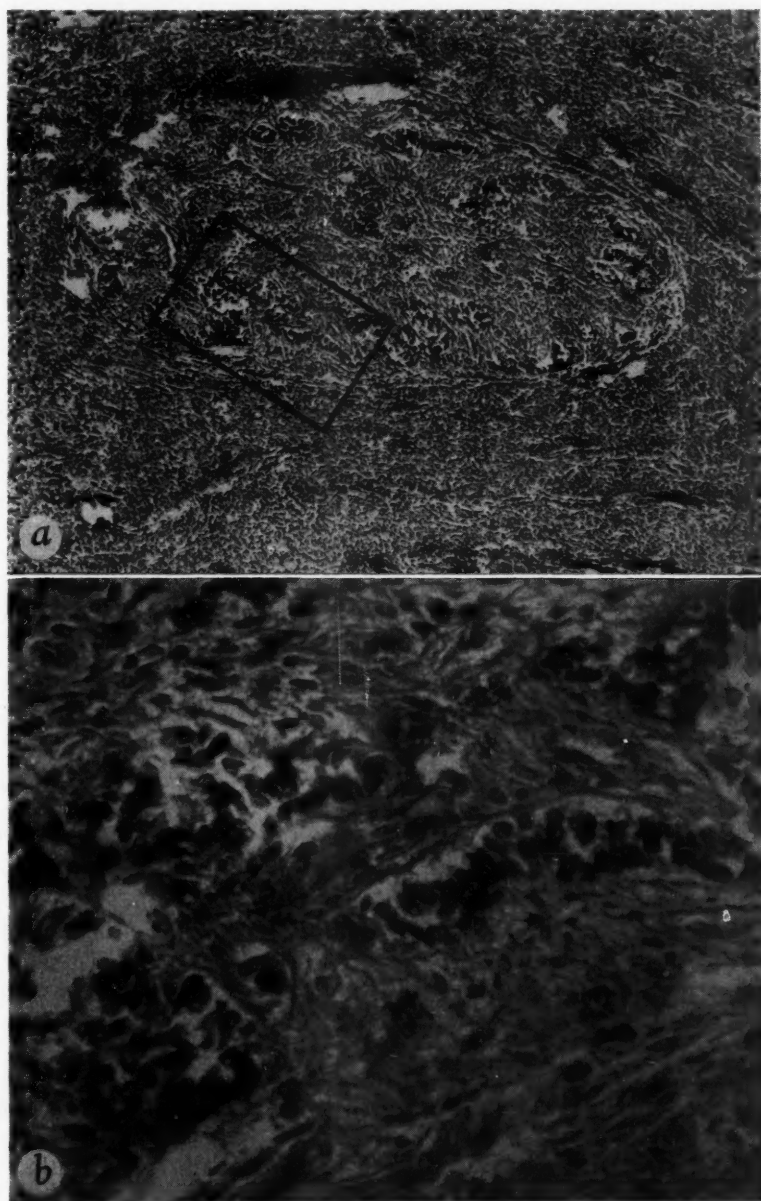


Fig. 7.—Case 13. *a*, An area encountered in a single section obtained deep in the tumor substance, showing clusters of darkly staining cells suggestive of an attempt to form glands and tubules. (Hematoxylin and eosin;  $\times 75$ .) *b*, Higher power view of same section, (Enlarged from  $\times 250$ .)



and 5, considerable inflammatory infiltration of the endometrial stroma was noted (Figs. 1, *d*, and 2). In Cases 1 and 2, microscopic foci of endometrial stroma were observed in the myometrium (Fig. 1, *b* and *c*). One of these foci resembled the invasive stromal processes encountered in cases of stromatosis or stromal endometriosis. Since changes characteristic of adenomyosis were noted in both cases, the stromal plugs may have represented adenomyosis in regions lacking in epithelial elements. That the condition described represents an extremely early example of stromatosis seems dubious, as the entire endometrium appears diffusely involved by the hyperplastic development. While the exact nature and the histogenesis of these bizarre hyperplastic stromal phenomena remain obscure, it might be postulated that they represent an abnormal stromal responsiveness to some stimulus, perhaps of hormonal or inflammatory origin. Whatever the cause, it appears that, particularly if the patient is relatively young, one should adhere rigidly to the histologic criteria suggested in the second paragraph of the section on Materials and Methods, for a diagnosis of sarcoma of the endometrial stroma; cellularity and mitotic activity alone are insufficient for this diagnosis.

*Proliferative Stromatosis (Stromal Endometriosis).*—The remaining 11 patients presented the condition that we have designated "stromatosis" as suggested by Novak,<sup>14</sup> although the term "stromal endometriosis" is well entrenched in published material. "Stromatosis" not only suggests that the tumors are relatively benign, but it avoids implying a relationship to endometriosis and adenomyosis, a connection that has yet to be conclusively demonstrated histologically.

The ages of the 11 patients with stromatosis, at the time of operation, ranged from 39 years to 68; the average age had been 45 years. Three of the patients (Cases 12, 15, and 16) had been well beyond the menopause. The symptoms had been those associated with other uterine neoplasms; namely, menorrhagia, metrorrhagia, postmenopausal bleeding, discharge, pelvic pain, and abdominal tumors. Three of the 11 patients had had rather pronounced secondary anemia.

Grossly, the lesions took the form of submucous and intramural pinkish-white, solid tumors of a rubbery consistency, with rootlike extensions which permeated the posterior or posterolateral uterine wall, the uterine veins and frequently the broad ligaments of the uterus (Figs. 3*a* and 6, *a*). On the cut surface, the ends of the invasive cords projected from spaces in the myometrium, thus providing the "comedo" or "rough towel" effect noted by Park.<sup>16</sup> Where long, wormlike ramifications of the tumor were found inside what appeared to be spaces lined with endothelium and occasionally inside veins, but evidence of destruction of the surrounding myometrium was lacking, the gross findings were considered to be, for all practical purposes, diagnostic. In the course of our study of stromal lesions we have not encountered any instance of sarcoma of high grade of malignancy extending in a similar gross fashion, even though microscopic evidence of venous and lymphatic invasion has been found frequently.

Histologically, the tumors presented a highly cellular composition of spindle cells, resembling endometrial stromal cells, but with remarkably invasive properties, including vasoinvasion (Figs. 4, *a*, *c*, and *d*, and 5, *a*). Mitotic activity was nil or minimal, and hyperchromasia and cellular pleomorphism were slight. The cells resembled those encountered in the stroma of the proliferative phase of the menstrual cycle and frequently were observed to be continuous with those of the normal endometrial stroma (Figs. 3, *c*, 4, *b*, and 6, *b*). The basal glands of the endometrium frequently were completely



surrounded by annular clusters of tumor cells. The intensification of vascularity was an outstanding feature of these cases; the vessels were thick walled, and about them the concentrically arranged stromalike cells often formed whorls (Figs. 2 and 3, *b*).

Of particular interest is Case 13. The tumor removed in this instance was considered characteristic, grossly and histologically, of the condition we chose to call "stromatosis." Yet in a single section obtained from a deep portion of the tumor we noted a tubular, glanduliform arrangement of darkly staining cells which suggested an attempt at epitheliogenesis (Fig. 7, *a* and *b*).

Case 8, in which the lesion was grossly typical of stromatosis, appeared to provide evidence for the stromal origin of these tumors. There was little evidence of mitotic activity; the cells were uniform in size and shape and frequently were disposed in cuffs around the numerous vessels (Fig. 4, *a*). In one section from the endometrial surface of the tumor, the cells not only were confluent with the endometrial stroma but also surrounded an endometrial gland (Fig. 4, *b*). Of even more interest are the sections obtained from a long intravenous extension of the tumor into the left broad ligament of the uterus. In Fig. 4, *c* are represented areas of benign osteoid tissue apparently arising from metaplasia of the stromal cells. In adjacent sections was benign, although rather cellular, osteogenic tissue, as is shown in Fig. 4, *d*. This is a low-power ( $\times 30$ ) cross section of the entire intravascular extension. We did not believe that the osteoid and osteogenic tissue in this tumor made obligatory the diagnosis of mesodermal mixed sarcoma, since it appeared benign in this instance and the remainder of the tumor appeared to be an example of relatively benign stromatosis. Despite the extensive pelvic involvement, the tumor had not recurred during the 6 years after operation, thus affording confirmatory clinical evidence of its benignancy.

Contrast to the previous cases, which were characterized in their gross features not only by sizable intramural and submucous tumors but also by extensive myometrial and vascular permeation, is found in Cases 14, 15, and 16. The tumors were broad-based polypoid lesions which invaded the myometrium but little as compared with tumors described in earlier paragraphs. Histologically, the tumors just now introduced are identical to the others with respect to cellular arrangement, epithelial inclusions, and vascularity. Although there is perhaps a little more hyperchromasia and mitotic activity, and slight morphologic variation of cells, there does not appear to be sufficient histologic evidence for an unequivocal diagnosis of sarcoma. Exactly where, then, should these tumors be classified? While they are certainly more active tumors than those previously described, we prefer to think that they are closer to the condition of stromatosis than to that of stromal sarcoma. They appear, however, to represent predominantly an exophytic type of growth rather than the typical endophytic type usually encountered in stromatosis.

### Treatment and Results

Table II gives the salient incidents of treatment in the 11 cases of stromatosis. Because of the extent of the disease in one case (fourth entry), only subtotal hysterectomy and bilateral salpingo-oophorectomy were feasible.

Treatment of 7 patients was successful; they have survived without recurrence from 5 to 14 years. One other patient (Case 15) died as the result of an unrelated illness after 7 years. Two additional patients are relatively recent, and have been available for follow-up only for 1 year (Case 11) and for 9 months (Case 12). The remaining patient (Case 10) died of uremia 4 years after the original treatment, despite multiple operative procedures and extensive roentgen therapy. At the time of her death there was no clinical

evidence of distant metastasis. With this exception, the clinical behavior of the tumors tends to confirm our original histopathologic impression of benignancy.

TABLE II. TREATMENT AND FOLLOW-UP: 11 CASES OF STROMATOSIS

PATIENTS	TREATMENT		RESULT	
	SURGICAL PROCEDURES	IRRADIATION	LIVING	DEAD
4	Total abdominal hysterectomy with bilateral salpingo-oophorectomy		5 years 6 years 9 months	After 7 years, of unrelated illness
3	Vaginal hysterectomy		14 years 9 years 1 year	
2	Vaginal hysterectomy with abdominal salpingo-oophorectomy		6 years 12 years	
1	Subtotal hysterectomy with bilateral salpingo-oophorectomy	600 mc. hr. of radium	9 years	
1	Subtotal hysterectomy, then excision of vesical recurrence done elsewhere. One year later, removal of cervical stump, left ovary, much of sigmoid colon; nine months after this, excision of vaginal recurrence	1,300 mc. hr. of radium; high-voltage roentgen therapy		After 4 years, of uremia, with local recurrence

### Comment

*Histologic Aspects.*—Although certain histologic aspects of the tumors under consideration seem to relate them to the larger group of endometrial stromal sarcomas, the clinically benign course followed seems to warrant placing them in a different, if adjacent, portion of the range of malignancy. Regarding stromal hyperplasia, our conclusions are simple enough. With full cognizance of the fact that glands whose appearance is either benign or malignant can be found in highly malignant endometrial sarcomas and carcinosarcomas, one yet should incline very strongly away from a diagnosis of endometrial sarcoma when such glands occur in a stroma which is not pleomorphic. Particularly should one hold to this inclination when the patient is a young woman.

Two findings among the cases of stromatosis deserve emphasis, namely, the occurrence of benign osteoid tissue, and the more than occasional presence of gland spaces and epitheliogenesis in cases of stromal endometriosis. The latter two have been reported by Park and Tennent,<sup>17</sup> Dougal,<sup>7</sup> and Goodall.<sup>10</sup> From previous studies by ourselves<sup>23</sup> and by others it is apparent that malignant endometrial stroma can, through metaplasia, become malignant bone and cartilage. It is suggested that the production of benign osteoid and epithelial tissue in these cases indicates that stromal endometriosis is at least stromal even if the "endometriosis" aspect is questionable.

The occurrence of glands within several of the lesions of stromatosis appears to offer a strong argument against identification of the tumors as hemangiopericytomas; this diagnosis has been suggested by Pedowitz and associates.<sup>18</sup> The hemangiopericytoma is a tumor derived presumably from cells

surrounding capillaries. These cells were designated "pericytes" by Zimmermann<sup>25</sup> and "extra-endothelial cells" by Clark and Clark.<sup>3</sup> It is possible that pericytes (whatever they are), being mesodermal, could create osteoid tissue, although a report of such development has not been made, as far as we know. Even the strongest proponents of the hemangiopericytoma, however, would question the ability of pericytes to produce glands. Neither would one expect pericytes to assume periglandular as well as perivascular distribution. Although it has been suggested that perivascular distribution is one of the diagnostic criteria of hemangiopericytoma,<sup>1, 13, 18</sup> Stout<sup>21, 22</sup> has noted that perivascular orientation of the pericytes is inconstant and inconspicuous and that the tumor is not organoid. Moreover, there is little gross pathologic similarity between tumors reported as uterine hemangiopericytomas and the hemangiopericytomas occurring in other regions.

*Clinical Aspects.*—Although probably the first description of a case of stromal endometriosis was published by Doran and Lockyer<sup>6</sup> in 1909 and the second by Casler<sup>2</sup> in 1920, much of the credit for publicizing the lesion must be ascribed to Goodall,<sup>10</sup> Robertson and co-workers,<sup>19</sup> Hunter,<sup>12</sup> and Park and Tennent.<sup>17</sup> For a complete discussion of the existing theories of histogenesis the reader is referred to the excellent paper of W. W. Park.<sup>16</sup>

Clinically, stromatosis is dissimilar to external endometriosis and adenomyosis in that it may occur after the menopause, it may recur and progress following castration, it is attended by no observed cyclic changes, and it forms distinct cellular masses that spread in a manner unlike that of endometriosis. We could find little histopathologic evidence to confirm a relationship to adenomyosis or to suggest that stromatosis represents malignancy arising in the stroma of adenomyosis. That some instances of stromatosis or even frank stromal sarcoma may arise in regions of adenomyosis or endometriosis appear plausible, since the parent cell may be dispersed not only throughout the uterine wall but wherever endometrial stroma is found.<sup>9</sup> The case reported by Ober and Jason,<sup>15</sup> in which there was multicentric origin of endometrial sarcoma in both the endometrial stroma and the stroma of external endometriosis, is of interest in this respect. Park,<sup>16</sup> who questioned the similarity of endometriosis and adenomyosis, suggested that the latter is a true neoplasm, having the same histogenesis as stromatosis, carcinosarcoma, and mesodermal mixed sarcoma.

We have devoted considerable attention to the pathology and classification of stromal neoplasms. That the subject is not entirely an academic one, but should be of interest to the clinician, can be emphasized by recalling that each of the 16 tumors reported had been classified previously as a stromal sarcoma, undoubtedly leading the clinician to offer the patient and family a dire prognosis.

From the surgical notes it is apparent that complete removal of the tumor was questionable in Cases 7, 8, and 12. Yet the 3 patients have survived for 9 years, 6 years, and 10 months following operation, without evidence of recurrence of their tumors. Late recurrence of their tumors does remain a possibility, however, for despite histologic evidence of benignancy, stromatosis sometimes may behave in a malignant fashion. Recurrences have been reported as much as 17 years following operation.<sup>16</sup>

It is impossible to ascertain the effect of radiation on stromatosis from a study of our cases. Only one patient (Case 10), late in the course of her disease, received adequate radiation and this was ineffective in halting progress of the condition. From published reports of cases it appears that the efficacy of irradiation is variable,<sup>5, 10, 16</sup> as is also true when this mode of therapy is

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utilized for sarcoma of the endometrial stroma. In several instances, especially the two cases noted by Corseaden,<sup>4</sup> the response to radiation has been dramatic. Since it is impossible to predict the response to irradiation, it seems logical to utilize high-voltage roentgen therapy in all cases in which complete removal of the tumor is subject to question and in cases in which the neoplasm has recurred. Where feasible, total abdominal hysterectomy and bilateral salpingo-oophorectomy appear to be the operation of choice. Even though the presence of ovarian tissue does not appear to influence the incidence of recurrence of the tumor<sup>16</sup> the oviduct and ovary may be involved by direct extension of the tumor (Case 12). If, however, the invasive stromatosis appears confined to the uterus, preservation of ovarian tissue does not appear to be particularly hazardous, and may be worth the risk if the patient is young. Not only is prognosis relatively good in the presence of tumors of this type but, in our entire study of stromal neoplasms, we have failed to encounter a recurrence or fatality resulting from a tumor classified as sarcoma, Grade I. Thus, it appears that, except in a case in which a stromal sarcoma is obviously of a high grade of malignancy, the patient may be offered a relatively good prognosis. Whereas the degree of invasion is of major prognostic significance when the tumor is a sarcoma of a high grade of malignancy, it is of little importance in prognosis for patients harboring sarcomas of low grade of malignancy and stromatosis. This is evidenced not only by our cases but by the observation of Park<sup>16</sup> that in 9 of 12 collected cases in which spread of the tumor was extrauterine, the patients were surviving without recurrence.

#### Summary and Inferences

In the course of a study of 56 uterine neoplasms previously classified as sarcomas of the endometrial stroma, we have encountered 16 hyperplastic lesions which we considered to be actually benign instances of stromal hyperplasia (5 cases) or tumors of a more aggressive character, perhaps bordering on a state of malignancy (11 cases). The latter seem to be examples of stromatosis (stromal endometriosis). It is suggested that inflammatory or perhaps hormonal stimuli may have resulted in a hyperplastic stromal reaction that may simulate the picture of early sarcoma arising in this tissue. If a patient is young and actively menstruating, one should be hesitant about diagnosing sarcoma of the endometrial stroma on the basis of a relative increase in cellularity or mitotic activity, especially if concomitant inflammatory changes in the stroma or mitotic activity in the epithelium should be observed. Demonstrable epithelial inclusions, areas of epitheliogenesis and osteogenesis, and continuity of the tumor with the endometrial stroma suggest a histogenetic relationship to other neoplasms derived from the endometrial stroma such as fibromyxosarcoma, carcinosarcoma, and mesodermal mixed sarcoma. The entire group of stromal neoplasms would appear to have a common ancestor in pluripotential mesodermal elements which in their various transformations can form a variety of tissue types. Evidence of a relationship between stromatosis and adenomyosis or that stromatosis represents a malignant process arising in the stroma of a lesion of adenomyosis could not be discovered. Similarly, it appears highly unlikely that a lesion of stromatosis, as has been suggested, is actually a uterine hemangiopericytoma, a poorly understood pathologic entity. We feel that many of the tumors previously reported as uterine hemangiopericytomas are in fact instances of stromatosis. We prefer to classify

the relatively benign stromal lesions here under consideration as instances of proliferative stromatosis, thus avoiding the serious prognostic connotation implied by the terms "sarcoma" and "malignant stromatosis." We suggest this, realizing that despite histologic evidence of benignancy, the tumors infrequently may behave locally in a malignant manner. At the time of writing of this report, of the 16 patients reported on (5 with stromal hyperplasia and 11 with stromatosis), only one had died as a result of direct extension of the tumor and 11 had lived for more than 5 years. Metastasis had not been encountered.

*Addendum.*—After this article was in press, we saw the contribution of Hunter, Nohlgren, and Lancefield (AM. J. OBST. & GYNEC. 72: 1072, 1956), in which they documented 2 cases of metastasizing stromal endometriosis. Prolonged survival of their 2 patients stands in marked contrast to the situation obtaining in cases of metastasizing endometrial stromal sarcoma.

### References

1. Begg, C. F., and Garrett, Rudolf: *Cancer* 7: 602, 1954.
2. Casler, DeW. B.: *Surg., Gynec. & Obst.* 31: 150, 1920.
3. Clark, E. R., and Clark, Eleanor I.: *Am. J. Anat.* 66: 1, 1940.
4. Corsecaden, J. A.: *Gynecologic Cancer*, ed. 2, Baltimore, 1956, Williams & Wilkins Company, pp. 392-393.
5. Da Cunha, F.: *J. Obst. & Gynaec. Brit. Emp.* 57: 633, 1950.
6. Doran, A. H. G., and Lockyer, Cuthbert: *Proc. Roy. Soc. Med. (Obst. & Gynec. section)* 2 (pt. 2): 25, 1909.
7. Dougal, D.: *Tr. New England Obst. & Gynec. Soc.*, Dec., 1926.
8. Finn, W. F.: *AM. J. OBST. & GYNEC.* 60: 1254, 1950.
9. Gilbert, B.: *Clin. Proc.* 2: 214, 1943.
10. Goodall, J. R.: *J. Obst. & Gynaec. Brit. Emp.* 47: 13, 1940.
11. Greene, R. R., and Gerbie, A. B.: *Obst. & Gynec.* 3: 150, 1954.
12. Hunter, W. C.: *Surgery* 34: 258, 1953.
13. McCormack, L. J., and Gallivan, W. F.: *Cancer* 7: 595, 1954.
14. Novak, Emil: *Discussion of Henderson, D. N.*: *AM. J. OBST. & GYNEC.* 52: 1000, 1946.
15. Ober, W. B., and Jason, R. S.: *A. M. A. Arch. Path.* 56: 301, 1953.
16. Park, W. W.: *J. Obst. & Gynaec. Brit. Emp.* 56: 759, 1949.
17. Park, W. W., and Tennent, R. A.: *J. Obst. & Gynaec. Brit. Emp.* 55: 423, 1948.
18. Pedowitz, Paul, Felmus, L. B., and Grayzel, D. G.: *AM. J. OBST. & GYNEC.* 67: 549, 1954.
19. Robertson, T. D., Hunter, W. C., Larson, C. P., and Snyder, G. A. C.: *Am. J. Clin. Path.* 12: 1, 1942.
20. Schiffer, M. A., Mackles, Abraham, and Wolfe, S. A.: *AM. J. OBST. & GYNEC.* 70: 521, 1955.
21. Stout, A. P.: *Cancer* 2: 1027, 1949.
22. Stout, A. P.: *Lab. Invest.* 5: 217, 1956.
23. Symmonds, R. E., and Dockerty, M. B.: *Surg., Gynec. & Obst.* 100: 232, 1955.
24. Symmonds, R. E., and Dockerty, M. B.: *Surg., Gynec. & Obst.* 100: 322, 1955.
25. Zimmermann, K. W.: *Ztschr. Anat.* 68: 29, 1923.

### Discussion

DR. J. MILTON SINGLETON, Kansas City, Mo.—A recent case in point which grossly appeared to arise in and display characteristics of a uterine tube was diagnosed arrhenoblastoma by one pathologist and highly undifferentiated carcinoma by two others including our own pathologist. The patient had severe hypertension before removal, and complete relief afterward. The associated symptoms suggested that the arrhenoblastoma diagnosis might be correct. It is interesting to consider that the missing or making of a diagnosis may rest upon the chance of seeing or not seeing one or two cells. The wonder is that we have men who are sufficiently dedicated to give time and effort to be almost always right. So it is not too surprising that the careful restudy of these cases has been so revealing. The authors' observations should be an added impetus to us all to review our pathological material and also to reconsider more often our past clinical results of all therapy.



I have found only one case reported from Kansas City similar to the cases reported here, a case by Dr. Jack Hill in *Archives of Pathology*, May, 1947. I am sure that a careful restudy such as the authors' may reveal more. A hint as to the diagnosis at the operating table might be the observance of wormlike masses in the broad ligament which are not varices.

With the growing tendency, increased by the vigilant tissue committee, to watch only the somewhat enlarged uterus through the climacteric, we all may be missing some of these as well as other interesting manifestations.

Certainly in the young woman who has many years of ovarian function possibly remaining, it is important that we be sure of the benign or malignant nature of the lesion prior to definitive therapy.

The authors mention hormonal influence and this forces me to show pictures of a very recent case of sarcoma-carcinoma somewhat related to the subject. Miss F. C., aged 62 years, had taken estrogens over a period of twenty years for an atrophic skin condition of the face and body. She reported having episodes of vaginal staining for three months. Pelvic examination showed a completely atrophic uterus and pelvic structures, and a Papanicolaou smear was negative. Prohibition of the estrogen resulted in cessation of the bleeding through a period of 5 months' observation and the uterus appeared even smaller. She was advised that recurrence would demand immediate curettage. She returned nine months after bleeding had recurred and the uterus was found to have ballooned to the proportions of a baseball.

This case calls attention to a mistake some of us make in delaying curettage or possibly laparotomy on any menopausal or postmenopausal patient who bleeds from any cause, and to the mistake of administering estrogens to this group except in cases of dire extremity.

DR. CARY M. DOUGHERTY, Baton Rouge, La.—Several years ago, when we encountered a few instances of this disease in the Louisiana State University gynecological pathology laboratory, we began to search in the literature for the experiences of others, and we got back to 1924, I think it was, for an article by Dr. Robert Frank. The name illustrates an important feature of this disease, "subendolymphatic hyperplastic proliferation."

In the very excellent kodachrome he had, I believe you can notice a single layer of endothelium, at least on one side of the mass of spindle cells, apparently with a vascular space of the myometrium. It was Dr. Frank's feeling that this was a subendolymphatic proliferation of the endothelium lining these spaces, and it has been the opinion of others that these masses of stroma cells probably burrow down in the interstices of the muscle bundles of the uterus and possibly bulge into the lymphatic or vascular spaces, where the going is a little bit easier. It was our opinion that patients did well on usual therapy without benefit of special treatment.

DR. PRATT (Closing).—From the study of our uterine sarcomas, it certainly seems that in the past, along with others, we have probably grouped too many cases under the diagnosis of endometrial sarcoma. Other people have also found 15 to 20 per cent of their "sarcomas" were actually benign lesions, and I think if we sent our slides around, it is very questionable if we would get any unanimous opinion as to which are sarcomas and which are not.

I feel that these 16 cases form an important group to separate off from the others, primarily from the point of view of prognosis. Ordinarily, we think of sarcomas of the endometrium as having a poor prognosis. We talk that way to the patient, and to the patient's family. We warn them about the outlook. And yet, if we can pick out this group of cases, then we can tell the patient and her family that the outlook is not hopeless, but that it is, instead, extremely good.

Incidentally, in the 5 cases of stromal endometrial hyperplasia, stromal hyperplasia, all have survived five years, and 10 of the 11 others have gone five years.



## DELAYED POSTPARTUM HEMORRHAGE\*

### A Review of 100 Cases at Harper Hospital

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THERE is little available information on this subject of delayed postpartum hemorrhage, in contrast to the more voluminous reports on the etiology and treatment of antepartum and immediate postpartum hemorrhage. Delayed postpartum hemorrhage in this study will be concerned with uterine hemorrhage that occurs within a few hours to several weeks following an uneventful puerperium of five or more days in the hospital.

The patient and the physician are more alert to the bleeding that accompanies gestation and its immediate termination. Vaginal hemorrhage occurring hours, days, or even weeks after dismissal from the hospital presents a situation that is difficult to explain to the patient and tends to make her and her family believe that the physician is at fault. Even though the best prophylactic measures in the prevention of hemorrhage have been followed during the prenatal, intrapartum, and immediate postpartum periods, delayed postpartum bleeding will appear in some cases.

McCartney<sup>7</sup> mentioned that late postpartum hemorrhage is caused by retained placental fragments or by abnormal involution of the placental site.

Gainey, Nicolay, and Lapi,<sup>1</sup> in a review of 8 cases of noninvolution of the placental site, believed that bleeding from a few hours to two weeks postpartum is diagnostic of such cases, but they also mentioned that multiparity and early ambulation might have some significance in delayed postpartum hemorrhage.

In a discussion of McNally and Baldwin's<sup>8</sup> presentation on "The Prophylaxis of Post-Partum Hemorrhage," Krebs stated that he had found an increase in delayed postpartum hemorrhage since patients have been permitted earlier ambulation and shorter hospitalization. Dorset, discussing this same presentation, attributed early ambulation, as well as the use of stilbestrol to inhibit lactation, as possible factors in causing this delayed bleeding.

Melody<sup>6</sup> mentioned a personal communication from Stephenson, who observed a definite increase in late postpartum hemorrhage even though the use of estrogens was avoided and there was no significant decrease in the number of mothers breast feeding their infants. Melody also suggested that early ambulation and full responsibility for the household on returning home might contribute to the increased incidence of delayed postpartum bleeding.

\*Presented at the Twenty-fourth Annual Meeting of the Central Association of Obstetricians and Gynecologists, New Orleans, La., Oct. 4, 5, and 6, 1956.

Parks, McLendon, and Kelley<sup>9</sup> emphasized the physiologic changes and physical fatigue following childbirth. They believed that, with the process of involution, the hyperactivity of the breasts, and possible disturbance in the excretory system, the mother's rest is considerably disturbed and the smoothness of convalescence may be hindered by "an unknown roommate . . ., variation in dietary habits; a new . . . bed . . ., and an unsolicited self-administered bath. . ."

As regards the common pathologic findings in late postpartum hemorrhage, Hansford and Weed<sup>2</sup> found that such bleeding resulted from either retained placental tissue or faulty subinvolution of the placental site. Wolfe and Pedowitz<sup>10</sup> claimed that in addition to these, there are two uterine factors present. In one there is a late separation of the thrombi at the placental site resulting in active bleeding and in the other uterine factor there is present an abnormal amount of decidua vera that causes the bleeding. Hansford and Weed also stated that uterine hypotonia, neoplasms, endometritis, and inversion of the uterus may also be contributing factors to this type of bleeding.

Leff<sup>5</sup> reported an undeveloped secondary embryo as a cause, since it is unabsorbed as pregnancy advances and is cast off at about the eighth to twelfth postpartum day.

Kurtz and Comando<sup>4</sup> reported 3 cases of uterine hemorrhage occurring one to one and one-half months post partum caused by placental polyps.

TABLE I. ANTENATAL STATISTICS

Average age	26 years
Term pregnancies	85%
Pregnancies of 36 to 38 weeks	10%
Parity.—	
Primigravidas	25%
Multigravidas	75%
Labor.—	
Average length	8½ hours
Induction	7%
Toxemia	3%
Previous rapid labor	2%
Dead fetus	1%
High Rh antibody titer	1%
Secondary inertia*	29%
Intravenous Pituitrin	7%
Analgesia.†—	
Demerol-scopolamine	45%
Demerol-scopolamine-barbiturate	34%
Anesthesia.—	
Spinal	53%
General‡	43%
Local	1%
None	3%

\*These patients received small dosages of obstetrical Pituitrin, or Pitocin in amounts from ½ to 1 minim intramuscularly for an average of two to three separate doses.

†None of these drugs were given in excessive amounts.

‡Through the Heidbrink Kinetometer machine.

This review of cases of delayed postpartum hemorrhage is concerned with patients who have been delivered uneventfully of a pregnancy of five months or more and who have had a normal puerperium up to the time of dismissal from the hospital but have to be rehospitalized within a few hours to a few

weeks because of moderate to severe uterine bleeding. Such cases were selected from the files of the Record Library of Harper Hospital, Detroit, bearing the final diagnosis of either subinvolution of the uterus, or uterine hemorrhage due to retained secundines.

A total of 100 cases were studied. The patients were admitted during the years 1947 through 1955.

The antenatal statistics are summarized in Table I.

The type of delivery, infants' weights, and a review of events in the third stage of labor are summarized in Table II.

TABLE II. THIRD STAGE OF LABOR

<i>Type of Delivery.—</i> Vaginal	98% (Intravenous ergot with anterior shoul- der in 13%)
Spontaneous	35%
Low forceps	57%
Midforceps	2%
Breech extraction	3%
Version and extraction	1%
Cesarean Section	3%
Previous section	2%
Placenta previa	1%
<i>Infants' Weights.—</i>	
2,500-3,600 grams	70%
4,000-4,500 grams	5%
<i>Third Stage.—</i>	
Average length	8½ minutes
Manual removal of placenta	11%
Expression of placenta after separation	89%
Ergot after placenta	87%

There was one twin pregnancy making a total of 101 deliveries, 98 of which were vaginal and 3 by cesarean section.

So far this study of the antepartum factors has shown nothing to suggest a significant cause for delayed postpartum hemorrhage. Before the immediate postpartum factors are analyzed, however, blood loss during delivery should receive some critical attention. There is always a tendency to underestimate blood loss.

TABLE III. IMMEDIATE POSTPARTUM FACTORS

<i>Estimation of Blood Loss.—</i>	
No estimation stated	38%
Minimal to 400 c.c.	57%
More than 500 c.c.	5%
<i>Time of Ambulation After Delivery.—</i>	
Within 24 hours*	85%
Within 48 hours	7%
Within 72 hours	5%
Within 96 hours	3%
<i>Oral Ergotrate, Post Partum.—</i>	
First 24 hours	46%
After 24 hours	33%
<i>Infant Feeding.—</i>	
Breast only	52%
Formula only	40%
Combined	8%
Stilbestrol to inhibit lactation	22%

\*Fifty-one per cent of these within the first 12 hours.

Table III summarizes the immediate postpartum factors such as estimation of blood loss, use of oral Ergotrate, type of infant feeding, and the use of stilbestrol.

Six cases of immediate postpartum hemorrhage were recognized and transfusions were given within at least the first few hours after delivery. Three additional patients received transfusions on the first, third, and fourth postpartum days, respectively. Probably more patients actually needed postpartum transfusions prior to their discharge from the hospital, but due to an afebrile, uncomplicated puerperium nothing more was done to determine this need until the patient returned with delayed postpartum bleeding.

There was a 6 per cent morbidity according to accepted standards of a temperature of 100.4° F. or above for 48 hours, exclusive of the first 24 hours following delivery. There were no deaths.

Table IV shows the length of stay in the hospital during the first admission.

TABLE IV. LENGTH OF STAY IN THE HOSPITAL ON FIRST ADMISSION

Less than 5 days	10%
5 days	27%
6 days	25%
7 days	24%
More than 7 days	14%

Table V summarizes the important statistics on the second hospital admission.

TABLE V. STATISTICS ON SECOND HOSPITAL ADMISSION

<i>Interval Between Discharge From Hospital And Readmission.—</i>	
Few hours to 24 hours	8%
2 to 7 days	25%
1 to 2 weeks	38%
3 to 4 weeks	17%
2 to 4 months	12%
<i>Condition and Treatment of Patients On Readmission.—</i>	
Patients in shock	9%
Patients transfused	47%
<i>Operations.—</i>	
Hysterectomy	2%
Curettage	95%
No operation	3%
<i>Histopathology.—</i>	
Decidual tissue	34%
Placental-decidual tissue	18%
Placental tissue	15%
Subinvolution	8%
Secretory endometrium	6%
Endometritis	6%
Proliferative endometrium	6%
Myometrium	3%

A total of 9 per cent of the patients on readmission were considered to be in shock. In only 7 per cent was the hemoglobin not recorded. Forty-five per cent had a hemoglobin of from 10 to 11 Gm. In 28 per cent the hemoglobin was recorded as under 9 Gm. and in 20 per cent the hemoglobin was over 12 Gm. Forty-seven per cent of the patients were given transfusions on readmission.

There was a 3 per cent morbidity on the second hospital admission and the patients were rehospitalized for an average of 4.4 days. There were no deaths.



### Comment

In analyzing the antepartum and intrapartum factors of these 100 cases, the following facts should be emphasized:

Seventy-five per cent of the patients were multiparas.

Intravenous Ergotrate during delivery of the anterior shoulder was given in only 13 per cent of the cases. Had this drug been given intravenously with the birth of the anterior shoulder routinely maybe there would have been a more complete shearing off of the placenta at the end of the third stage and therefore a decreased tendency toward delayed vaginal bleeding.

In 11 per cent of the cases the placenta was manually removed. According to Hawkins,<sup>3</sup> in over 3,000 cases in which routine exploration of the uterus was carried out following delivery, only one patient returned to the hospital because of bleeding. Maybe more patients should have manual exploration of the uterus following delivery, provided there is a missing cotyledon or retention of an accessory lobe, or there is reason to suspect injury to the uterine cavity.

As in functional uterine bleeding, there is no histological picture that is pathognomonic of delayed postpartum bleeding.

As was previously mentioned, some of our colleagues have thought that early ambulation may be a factor in delayed postpartum hemorrhage. With the increased number of obstetrical admissions and the shortage of hospital beds as well as the shortage of nursing personnel, the obstetrician has been forced to encourage much earlier ambulation than he did fifteen years ago. Early ambulation was popularized at that time by the surgeons who claimed that with such a routine the postoperative incidence of vascular complication was much less. Prior to fifteen years ago the parturient was given leg exercises and deep breathing exercises during her confinement in bed for the first week following delivery. There is little convincing evidence in the field of obstetrics that these patients had any more vascular complications than those who are at present walking about within the first 24 hours after delivery. With the advent of chemotherapy, the use of antibiotics, the availability of matched blood, and the improved methods of anesthesia, the pregnant patient has little chance of developing thromboembolic complications in the postpartum period. It is true that the parturient was confined to bed longer than necessary, but now perhaps we have gone to the other extreme in allowing her to walk so early. Perhaps the time for ambulation should be related to the rapidity of involution, with the patient remaining in bed until the fundus can be felt to be at least halfway between the umbilicus and the pelvic brim and the lochia ceases to be a profuse rubra type. In the meantime the patient can sit on the edge of the bed and swing her legs two or three times daily before ambulation begins.

The management of the parturient and the recent postoperative gynecological patient should differ. Little regard is given to the preceding events that the parturient has experienced, such as the nervous, emotional, and physical strain imposed by her gestation. At the time of her delivery the assessment of blood loss is given little thought in comparison with the immediate and sometimes unnecessary replacement of blood in a patient who has elective hysterectomy. There is little regard for the persistent slow loss of blood during the puerperium and reliance is placed on oxytocics instead of a re-evaluation of the hemoglobin and red-cell count before dismissal from the hospital. The surgical patient has a much better chance for rest in the hospital and on

her return home than has the parturient, whose rest may be disturbed many times in 24 hours by the regular feeding schedules and other demands of her infant, especially if she is permitted or advised the rooming-in plan.

### Conclusions

One hundred cases of delayed postpartum hemorrhage at Harper Hospital during the years 1947 through 1955 were selected for study.

There were no specific antepartum factors that could be assigned to the exact etiology of this type of bleeding.

Ergot preparations given intravenously with the birth of the head or anterior shoulder, together with slow delivery of the baby, may bring about a more complete shedding of the placenta and its membranes and thus prevent greater blood loss at the end of the third stage and later in the puerperium.

Blood loss is underestimated. Postpartum blood counts should indicate the necessity for blood transfusions prior to discharge from the hospital.

The routine exploration of the uterus following the third stage of labor is not going to prevent delayed puerperal bleeding caused by retention of of decidua or by late separation of thrombi from the placental site.

Ambulation may be delayed until there is evidence of a firm uterus located halfway between the umbilicus and the pelvic brim. Young patients with uncomplicated deliveries are not prone to develop thromboembolic complications because they have been kept in bed for the first 48 or 72 hours for a short rest that has been well earned.

Ninety-seven per cent of the cases required surgical interference to control the bleeding.

The common histopathological picture is that of retained decidua and/or placental tissue or subinvolution of the placental site.

The patient on returning home should be provided with adequate assistance for at least two weeks.

A continuation of a well-balanced high-protein diet, plus the necessary iron and vitamin supplements, is important. Thyroid extract given as indicated during the prenatal period may have as logical an empiric use in the postnatal period.

The cost of rehospitalization for delayed postpartum hemorrhage exceeds the cost involved in keeping the patient a few extra days in the hospital for a more thorough evaluation of her physical status.

Maybe these cases should be observed in the future with studies of bleeding and clotting time, blood dyscrasias, and hypofibrinogenemia.

### References

1. Gainey, H. L., Nicolay, K. S., and Lapi, A.: *AM. J. OBST. & GYNEC.* 69: 558, 1955.
2. Hansford, D. P., and Weed, J. C.: *Obst. & Gynec.* 1: 317, 1953.
3. Hawkins, R. J.: *AM. J. OBST. & GYNEC.* 69: 1094, 1955.
4. Kurtz, G. R., and Comando, E. N.: *AM. J. OBST. & GYNEC.* 66: 663, 1953.
5. Leff, M.: *West. J. Surg.* 56: 448, 1948.
6. Melody, G. F.: *Am. J. Surg.* 78: 821, 1949.
7. McCartney, C. P.: *M. Clin. North America* 38: 265, 1954.
8. McNally, H. B., and Baldwin, Wm.: *South. M. J.* 48: 793, 1955.
9. Parks, J., McLendon, P. A., and Kelley, M.: *AM. J. OBST. & GYNEC.* 66: 938, 1953.
10. Wolfe, S. A., and Pedowitz, P.: *AM. J. OBST. & GYNEC.* 53: 84, 1947.

### Discussion

DR. ANTHONY RUPPERSBERG, JR., Columbus, Ohio.—In the Ohio State University Health Center from 1950 through 1955, there were 18,235 deliveries of pregnancies of from five months to term. During the same period of time there were 172 patients (or

0.94 per cent of the total number of deliveries) admitted through the Gynecology Division because of postpartum (or postabortal) hemorrhage due to either retained secundines or subinvolution. Their pregnancies were terminated at various periods ranging from five months to term. Of the 172 patients admitted, 154 (89.5 per cent) of them were subjected to curettement.

Even though this incidence may seem low, it is obvious that we should seek for methods to reduce it. We believe that certain measures employed to prevent *immediate* postpartum hemorrhage, will also prevent *delayed* postpartum hemorrhage, since there is obviously no single etiological factor connected with the latter. Hence we incorporate the following points in our teaching program:

1. *Ante Partum.*—In the multiparous patient, the *history* of postpartum hemorrhage connected with a previous delivery (Robert Willson) should provoke high suspicion. Therapy should include a well-rounded diet, with supplements of vitamins C, K, P, and B complex. The patient should be carefully watched to avoid excessive gain in weight, and in the last week of pregnancy the hemoglobin and red count should be checked; severe anemia should be corrected by transfusion. Toward term, we make a mental note in a case where the uterus is overdistended with polyhydramnios, twins, or a large fetus, to watch the patient especially for hemorrhage.

2. *Intra Partum.*—Every effort is advanced to prevent precipitate delivery; an attempt is made to effect a gradual delivery of the fetus, allowing the fundus to "follow down" after the superior pole.

3. *Post Partum.*—

a. *Early:* Routinely we administer Pitocin, 1 c.c. intramuscularly, with the delivery of the anterior shoulder in the cephalic presentation, and reserve Ergotrate (1/320 grain) for intravenous administration after the placenta is delivered. As a rule, an attempt is made to estimate blood loss accurately *at once*; if the amount is estimated to exceed 500 c.c., a 16 or 18 gauge needle is immediately inserted into the patient's vein, blood is withdrawn for cross-matching with the unit of blood on order, and parenteral fluids are administered until the blood arrives. Usually we start a container of 5 per cent dextrose solution in distilled water containing 1 c.c. of Pitocin as a routine postpartum measure in the following instances: (1) overdistended uterus; (2) following delivery after a long, desultory labor, with dehydration of the patient; (3) where the patient has had extended induction of labor, using the Pitocin drip; (4) where ether or chloroform anesthesia was employed intrapartum.

If the quantity of bleeding from the birth canal obscures visibility of the area to be repaired, the area of hemorrhage should be located, and the hemorrhage controlled before repair is attempted! Investigation should include the corpus, cervix, vagina, and perineum, in that order. We agree with Hawkins that the uterus should be explored manually for rupture, secundines, polyp, or neoplasm. For those who do not agree that it should be employed as a routine measure after *every* delivery, certainly exploration should be done where there is immediate postpartum hemorrhage! In the case of uterine atony in the immediate postpartum period, the uterus should be elevated out of the pelvis, it should be anteverted, and massaged. If it bleeds in spite of these measures, including the "Pit drip," a 12 yard pack is inserted. If the patient then bleeds through the packing, hysterectomy is indicated. We advocate *early diagnosis* and *active intervention* to curtail immediate postpartum hemorrhage, and to prevent delayed postpartum hemorrhage. As Hollenbeck and others have said, the problem resolves itself into "masterful activity versus muddle-some midwifery."

b. *Late:* Routinely Ergotrate is administered, especially to nonnursing mothers, for from three to four days post partum. We encourage frequent change of the patient's position in bed for the first two days, and early ambulation on the third postpartum day, unless there is a marked subinvolution of the uterus. The hemoglobin of the postpartum patient should be examined routinely before she departs from the hospital.

DR. E. L. KING, New Orleans, La.—We believe in the intravenous administration of ergot preparations in cephalic presentations of the anterior shoulder. We think it helps decrease immediate hemorrhage. Afterward, patients are generally given an ergot preparation for 24 or 36 hours, as a matter of routine.

I do not think that early ambulation has been a factor in postpartum hemorrhage. The patient gets out of bed in 24 hours, and sometimes earlier. She goes home about the fourth or fifth day. As I remember, we have not had any delayed postpartum hemorrhages since we have been using early ambulation.

DR. ALWYN E. BENNETT, Cleveland, Ohio.—As to the point of early ambulation, I do not think that, primarily, it is early ambulation, itself, that is important. I think it is the amount of that early ambulation. Getting up and going to the bathroom is one thing; getting up and taking a shower and making the children's bed when the patient gets home is something else.

The second point—I think routine Ergotrate in a normal patient is one thing, intravenously or intramuscularly; routine Ergotrate in a patient who has hypertension or who has a markedly elevated blood pressure, or possibly cardiac disease, may be a dangerous drug, and I think, with care, those patients should probably not be given intravenous Ergotrate, post partum, particularly if they have spinal anesthesia, because the blood pressure may rise to untold heights after Ergotrate.

We are very averse to packing a uterus, post partum. Ordinarily, I think if the uterus does not respond with the Ergotrate, a hand introduced into the uterus will many times save time and blood. The uterus will contract firmly on the hand, or it will not. If it contracts well, there are no foreign bodies; the hand can be withdrawn quickly, and the patient is safe. If the uterus remains flabby and soft, packing will only delay a possible hysterectomy, and probably increase the risk to the patient.

DR. JAMES B. ESKRIDGE, Oklahoma City, Okla.—We have also been somewhat concerned with the delayed postpartum hemorrhage—by that I mean 10 to 15 per cent of the patients who have curettages, who, despite the pathological report, will have a recurrence of hemorrhage.

DR. C. PAUL HODGKINSON, Birmingham, Mich.—About ten years ago we were plagued with the problem of delayed postpartum hemorrhage to an inordinate degree, but in the last few years we have had less trouble. We stopped giving stilbestrol to the patients, and we stopped using Ergotrate routinely for the first 24 or 48 hours following delivery. It seems to me that we have had less trouble since we have followed that new routine.

That may not seem consistent in the light of the following remarks, because I have also been interested in the question of ambulation, and whether or not ambulation does increase the tendency of patients to bleed. Despite the fact that we may not have any good reasons to believe that putting a patient to bed may decrease the tendency toward hemorrhage, certainly, from an empirical standpoint, that is one of the most important things done.

I think we fail to differentiate as to whether or not the patient is having arterial or venous bleeding, which I think is a very important point for consideration.

The uterus controls itself from exsanguinating hemorrhage through the process of contraction. A patient can have totally incoagulable blood and yet not bleed to death so long as the myometrium contracts.

This problem of the myometrial contraction was the one thing which delayed the investigation of the arterial blood supply of the endometrium many years ago. It was discovered that, in order to get an opaque medium into the arterioles of the endometrium, the substance had to be given *in vivo*.

This is not true on the venous side. One can certainly inject the venous side of the uterus with no difficulty whatsoever, with relatively slight pressure. In testing that, we



use relatively low pressure, just 15 cm. of water pressure in the extirpated uterus, and you can inject the venous pattern of the myometrium with no difficulty whatsoever.

We found that the central venous pressure was raised by many things, such as holding the breath, or coughing, or straining, and that is transmitted directly to the endometrium. I wonder if this is not a factor in some of these cases of hemorrhage following delivery? And in case the decidua has not recovered sufficiently to support this added venous pressure, perhaps bleeding occurs for that reason.

DR. HEATH (Closing).—As to the question on the recurrence of bleeding after curettage, I know we have had some cases, and I think that occurs with everyone. Maybe it is because we did not do a very thorough curettage, to begin with, because we were too timid.

Dr. Hodgkinson's remark on the subject of venous pressure is very interesting, but I am sure I cannot speak with any experience on experiments along this particular phase of his work.

## THE PREVALENCE OF VAGINITIS\*†

### A Study in Incidence

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VAGINITIS is the most common disease of the female genital tract and therefore is of great social, economic, and medical importance. Published reports on vaginal infections deal primarily with trichomoniasis and moniliasis, with so-called "nonspecific" bacterial vaginitis receiving scant attention. There have been few studies comparing the incidence of these three prevalent types of infection from the different socioeconomic levels within a given geographic area. Not only has there been a broad diversity in selection of patient material, but the methods and criteria for establishing diagnoses have varied greatly among different investigators.

The chief purpose of this study was to determine the incidence of the major infectious vaginitides in groups of patients from various levels of socioeconomic standing within a given population.

### Materials and Methods

All clinical observations on private patients were made by H. L. G. and on clinic patients by T. K. D. All stained-smear microscopy and culture interpretations were made by C. D. D. All wet mounts from both private and clinic patients were examined by the same medical technologist.

*Patient Material.*—This study comprises an investigation of the vaginal status of 2,251 white patients from a private office practice and 993 unselected clinic patients, white and Negro, from the obstetrical and gynecological outpatient clinics of Jefferson Davis Hospital. This institution cares for the indigent of Harris County. There was no selection of patients on the basis of presenting symptoms. Usually, no attempt was made to evaluate patients who were bleeding or who had not abstained from douching for one or more days. Practically all private patients had abstained from douching and intercourse for three or more days when evaluated. Patients who developed vaginitis subsequent to the evaluation examination were not included in the incidence.

*Clinical Observations.*—The gross characteristics of vaginal secretions which we consider of diagnostic value include: volume, color, odor, frothiness, consistency, and pH. An odorous, gray, homogeneous vaginal secretion of pH 5.0 or greater in women of childbearing age, who are not immediately postpartum, denotes the presence of *Trichomonas vaginalis* or *Haemophilus vaginalis*. Because of the close similarity of gross characteristics of the discharges,

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differentiation between *Trichomonas vaginitis* and *H. vaginalis vaginitis* is dependent on laboratory methods. Many foul-smelling, homogeneous discharges with a pH less acid than normal yield no trichomonads, but heavy fields of short gram-negative bacilli and numerous distinctive epithelial cells characteristic of *H. vaginalis vaginitis*. These cells have been previously described<sup>1</sup> and designated "clue cells." A slightly curdy, white vaginal secretion without disagreeable odor and with a pH of 4.7 or less indicates a normal bacterial flora, with or without the presence of *Candida*. Candidal infections are usually associated with a curdy type of vaginal secretion, with or without thrush patches.

The most frequent gross pathological changes of the vulva are redness and/or edema, and these findings are indicative of trichomoniasis or moniliasis. Redness of the vagina suggests trichomoniasis or moniliasis, while vaginal petechiae and swollen papillae indicate trichomoniasis. *H. vaginalis* rarely produces gross pathological changes of the vulva or vagina.

Vulvar itching, burning, chafing, or other symptoms of irritation are usually the result of moniliasis or trichomoniasis and are rarely produced by *H. vaginalis*.

**Laboratory Studies.**—The extent of laboratory work performed on individual patients was governed by clinical indications and routine wet mount findings. Seven hundred thirty of the 2,251 private patients and 754 of the 993 clinic patients were studied bacteriologically. Material for culture was taken on a small dry, cotton-tipped applicator from the vaginal vault ahead of the spread blades of a boiled, unlubricated bivalve speculum, and this was suspended in 1.0 ml. of sterile thioglycolate broth. Transfers from the broth were made to appropriate media as indicated clinically or microscopically. Trichomonal cultures were not employed routinely in this study. The most satisfactory medium to date for culturing *H. vaginalis* has been a modified Casman's blood agar,<sup>2</sup> employing 5 per cent rabbit blood and incubated under increased carbon dioxide (candle jar) at 37° C.

After material was obtained for culture, the speculum was then inserted the full distance of the vagina and all material possible collected on the lower blade. Using Hydrion paper, a pH determination was made from the material on the withdrawn speculum. Earlier in the study of private patients pH determinations were made by applying the paper to a lateral vaginal fornix. The Hydrion paper method for determining pH has proved satisfactory for all practical purposes.

A wet mount prepared from each patient was examined as a routine screening procedure. From private patients, these were prepared by obtaining vaginal secretions on a moistened cotton-tipped applicator. The material was mixed with a drop of physiological saline on a glass slide and a cover slip applied. For convenience, wet mount suspensions from clinic patients were made from vaginal material suspended in 0.5 ml. of physiological saline. The wet mounts were examined primarily for motile trichomonads, epithelial "clue cells" of *H. vaginalis*, spores and filaments of *Candida*, type and variety of bacteria, the relative number of pus cells, and the relative number of immature epithelial cells.

Gram stain was used on all smears of vaginal material, and in addition Giemsa stain was used if granuloma inguinale or fusospirochetal infection was suspected clinically or microscopically.

The diagnosis of moniliasis was not made on incidental positive smears and cultures in the absence of gross or subjective evidence of the disease. We consider *Candida* a normal inhabitant of the vagina which produces clinical moniliasis only when the vaginal environment becomes optimal for its rapid multiplication.

Conferences were held at intervals between clinicians, bacteriologist, and technologist to correlate the independent findings and classify the vaginal status of each patient.

### Findings

This report concerns the infectious vaginitides, and of these trichomoniasis, moniliasis, and *H. vaginalis* vaginitis constituted the vast majority. Atrophic vaginitis, while possibly representing a disease entity, is not regularly associated with a specific pathogen. Therefore, only those patients with atrophic vaginas who yielded specific pathogens are included in the incidence.

We had originally planned to compare the findings of this study with those from other areas, but it was soon evident that to draw comparisons with meaning would be exceedingly difficult because of the varied methods of selecting patient material and because of the great variation in laboratory methods employed. It suffices to say that the incidence of trichomoniasis and moniliasis in the various groups included in this study appear to fall within the extremes of other reported results. While in general the incidence of vaginitis in the private patients compares favorably with that of similar groups in other reports, the incidence in clinic patients for each category approaches the highest previously reported.

*Incidence in Extremes of Socioeconomic Standing.*—It can be assumed that private white patients who seek specialty care represent those with the greatest social and economic advantages and that the extreme opposite group is composed of patients attending public charity clinics. The corrected incidence of vaginitis in the private white group was 23.2 per cent, while the incidence in the clinic group composed of white and Negro patients was 69.3 per cent, a threefold difference (Table I). These are corrected figures giving the number of patients with vaginitis and do not represent the total number of vaginal infections. A large number of patients, particularly from the clinic group, had multiple infections with as many as five unrelated pathogens isolated from a single vagina. The highest incidence was in the subgroup composed of non-pregnant Negro clinic patients. Of the 352 patients in this group, 83.8 per cent had vaginitis and 20 per cent of them yielded two or more specific pathogens. The total number of specific infections in this Negro clinic group averaged 1.1 per patient.

The incidence of vaginitis in the white clinic patients fell midway between the private white and the Negro clinic groups (Tables I and II).

TABLE I. INCIDENCE OF VAGINITIS IN 2,251 WHITE PRIVATE PATIENTS AND IN 993 CLINIC PATIENTS

	PRIVATE GROUP		CLINIC GROUP					
	WHITE		WHITE (325)		NEGRO (668)		TOTAL CLINIC	
	CASES	%	CASES	%	CASES	%	CASES	%
<i>H. vaginalis</i>	274	12.2	62	19.1	227	33.9	289	29.1
Trichomonas	182	8.1	96	29.5	303	45.3	399	40.2
Candida	111	4.9	29	8.9	99	14.8	128	12.9
Miscellaneous bacteria	16	0.7	12	3.7	34	5.1	46	4.6
Total infections	583		199		663		862	
Mixed infections	60		29		145		174	
Patients with vaginitis	523	23.2	170	52.3	518	78.2	688	69.3

*Effects of Pregnancy on Incidence.*—Practically all investigations have shown the incidence of vaginitis to be higher in nonpregnant patients, and this is confirmed by the results of this study (Table II). The three most common



vaginal pathogens, *Trichomonas*, *H. vaginalis*, and *Candida*, thrive in the vaginas of estrogen-secreting women. Therefore, the hyperestrogenic state of pregnancy is not fully acceptable as an explanation for this difference. A more logical explanation would be that obstetrical patients as a group are younger and have had fewer years to acquire infections. It is probable also that promiscuity decreases with an enlarging abdomen and thoughts of motherhood.

TABLE II. INCIDENCE OF VAGINITIS IN PREGNANT AND NONPREGNANT PATIENTS

	PREGNANT						NONPREGNANT					
	WHITE PRIVATE (1,047)		WHITE CLINIC (176)		NEGRO CLINIC (316)		WHITE PRIVATE (1,204)		WHITE CLINIC (149)		NEGRO CLINIC (352)	
	CASES	%	CASES	%	CASES	%	CASES	%	CASES	%	CASES	%
<i>H. vaginalis</i>	106	10.1	33	18.7	83	25.9	168	14.0	29	19.3	144	40.9
<i>Trichomonas</i>	60	5.7	35	19.9	115	36.4	122	10.2	61	43.6	188	53.5
<i>Candida</i>	60	5.7	24	13.6	66	20.9	51	4.3	5	3.4	33	9.4
Miscellaneous bacteria	4	0.4	6	3.4	14	4.4	12	1.0	6	4.0	20	5.7
Total infections	230		98		278		353		101		385	
Mixed infections	20		15		55		40		14		90	
Patients with vaginitis	210	20.0	83	47.2	223	70.5	313	26.1	87	58.4	295	83.8

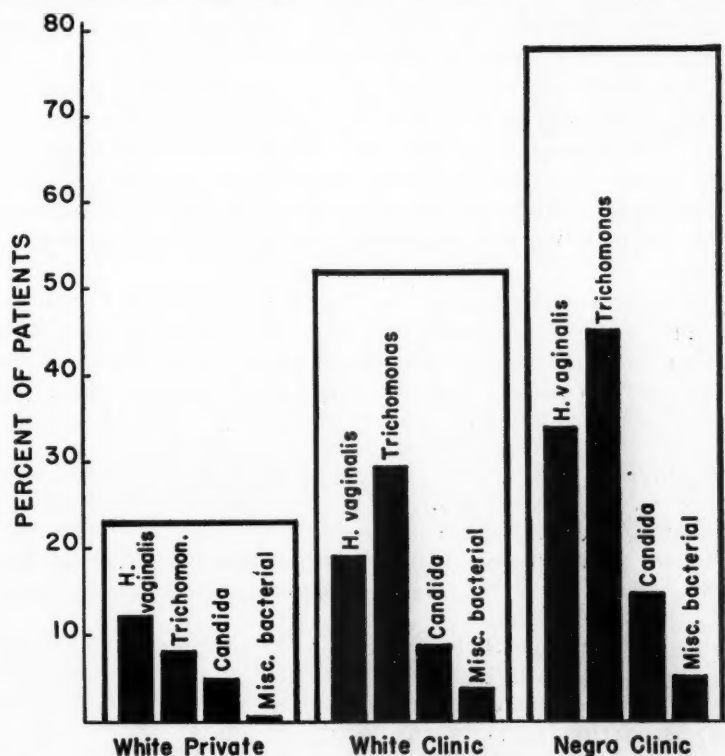


Fig. 1.—Graphic representation of the relative incidence of the infectious vaginitides in the groups studied.

*Haemophilus Vaginalis* Vaginitis.—In 1955 we<sup>1</sup> (H. L. G. and C. D. D.) published evidence that the great majority of so-called "nonspecific" vaginitides comprise a specific infectious entity, ascribable to a single bacterium, *Haemophilus vaginalis*. The infection has a definitive clinical pattern characterized by the presence of a gray, homogeneous, odorous discharge of pH 4.8

to 5.5. Table I shows that 94.5 per cent of all cases of bacterial vaginitis in the private white patients and 84 per cent in clinic patients were attributable to *H. vaginalis*. The majority of the remaining bacterial infections were attributable to other identifiable pathogens. Previously these patients would have had diagnoses of "nonspecific" bacterial vaginitis. The results of this study indicate that *H. vaginalis* is the most common pathogen in the causation of vaginitis in private white patients in the Houston area. *H. vaginalis* has been isolated as the predominant vaginal organism in numerous patients who recently had arrived in Houston from distant states and foreign countries.

**Moniliasis.**—The incidence of moniliasis was 4.9 per cent in private patients and 12.9 per cent in clinic patients. The greatest subgroup variation was seen in clinic patients and it ranged from 3.4 per cent in white nonpregnant patients to 20.9 per cent in Negro pregnant patients (Table II). Nonpregnant private patients are prone to seek immediate medical attention for the pruritus of moniliasis and this probably explains the relatively close ratio between the pregnant and nonpregnant patients of this group. The statistics for all groups are based on initial examinations but it must be assumed that many others, particularly in the private pregnant group, developed infections during the subsequent course of pregnancy. The majority of the private patients were evaluated in the first trimester, while the majority of clinic patients were evaluated in the second or third trimester of pregnancy. *Candida albicans* and *Candida tropicalis* were the most frequently isolated species.

**Relative Incidence of *H. Vaginalis* Vaginitis and *Trichomonas* Vaginitis.**—It is shown in Table I that the ratio between the incidence of *H. vaginalis* vaginitis and that of *Trichomonas* vaginitis differs in the private and clinic groups. The *H. vaginalis* to *Trichomonas* ratio for private white patients was 3:2, while the ratio in the clinic Negro group was 3:4. We offer no explanation for the reversed ratio between these infections in the two extremes of socioeconomic standing.

**Miscellaneous Infections.**—Under this heading are included chancroid, gonorrhea, granuloma inguinale, fusospirochetal, beta hemolytic streptococcal, and a few unclassified infections. The incidence of miscellaneous infections in the private group was 0.7 per cent as compared to 4.6 per cent in the clinic group. A total of 24 (2.4 per cent) clinic patients yielded bacterial findings typical of Vincent's infection. Most of these patients showed no ulcerations but all had foul-smelling discharges. The majority were associated with either trichomoniasis or *H. vaginalis* vaginitis. Many vaginas in the clinic patients constituted veritable microbiological museums with bacteria such as *Vibrio*, various spirochetes, fusiform bacilli, and large gram-positive streptobacilli frequently appearing in the flora. These organisms were rarely encountered in the group of private patients.

Three private patients had beta hemolytic streptococcal infections. Each had subjective symptoms of irritation, a serous discharge, and acute redness of the vagina and 2 yielded pure cultures of the organism. Two of the patients were six weeks postpartum, and one was postmenopausal.

Soon after undertaking the laboratory study of clinic patients, we were better able to understand the frustrations which have plagued many competent bacteriologists whose clinical material has been limited to clinic patients. Frequent problems in bacteriological diagnosis were encountered in clinic patients which rarely appeared in the private group. For example, a much larger variety of organisms was encountered in the clinic group and the isolation of *H. vaginalis* in pure culture was exceptional. Pure cultures of *H. vaginalis* were frequently obtained from private patients.

### Comment

This report serves to emphasize the over-all prevalence of vaginitis and the great variation in incidence between different socioeconomic groups. The findings clearly demonstrate that vaginitis becomes progressively more common as indigency increases. The factors contributing to this great difference undoubtedly are numerous and varied. Promiscuous sexual habits and poor genital hygiene must play important roles if the opinion is correct that *Trichomonas vaginitis* and *H. vaginalis* vaginitis are transmitted by sexual intercourse.

The unavailability of medical care is not acceptable as the major factor accounting for the difference in incidence, particularly in metropolitan areas where well-staffed clinics are available to the poorer classes. Perhaps women with social and educational advantages are more prone to seek medical care than indigents who are apt to accept vaginal discharges and minor irritations as being trivial or normal.

In consideration of the high incidence of vaginitis and the associated disagreeable odors, it is easy to understand the lay impression that all vaginas are tainted and in need of frequent douching. While *H. vaginalis* vaginitis has probably contributed as greatly to this common opinion as any other condition, it does not present a serious therapeutic problem. Trichomoniasis, on the other hand, has remained an obstinate problem in spite of the large number of therapeutic preparations which have been developed. It has been our experience that no more than a small percentage of patients can be freed of trichomonads by any method presently available whether it be by topical application or oral administration.<sup>3</sup>

Vaginitis, in addition to its socioeconomic connotations, is a disease of esthetic and physical importance and one which is contributing materially to psychosexual problems. Postcoital irritation of the penis resulting from vaginal infections is more common than is generally recognized. Vaginal itching and tenderness, dyspareunia, and resulting emotional irritability all contribute to psychosexual maladjustments. Vaginitis, exclusive of moniliasis, is usually associated with a disagreeable odor, and this is a fact of which the patient is too often ignorant and the husband acutely conscious.

It can be concluded that vaginitis with all its physical discomforts and esthetic objections constitutes something of a medical enigma which deserves increased concern and attention. The problem in many respects approaches the deplorable for a modern age.

### References

1. Gardner, H. L., and Dukes, C. D.: AM. J. OBST. & GYNEC. 69: 962, 1955.
2. Casman, E. P.: Am. J. Clin. Path. 17: 281, 1947.
3. Gardner, H. L., and Dukes, C. D.: Obst. & Gynec. 8: 591, 1956.

### Discussion

DR. KANE ZELLE, Springfield, Ill.—Vaginitis with its accompanying leukorrhea is probably the most common, and certainly the most annoying, problem confronting the

gynecologist in office practice. The increasing emphasis in recent years on routine prophylactic gynecological examination has been implemented by new chemical, bacteriological, and microscopic techniques. These have been of value not only in local diagnosis and treatment, but also in revealing the presence of underlying pelvic pathology. Any further information on the etiology of vaginal discharge is therefore of great importance.

Dr. Gardner has presented a most interesting and painstaking study of the incidence of vaginitis in patients of various socioeconomic levels in the Houston area. I feel that such a study is a valid sampling particularly on the private patient group. That a larger percentage of white clinic patients in another area would affect the clinic ratios seems likely.

Most striking is the threefold difference in incidence between the white private and Negro clinic patients. The author points out that personal hygiene and sexual promiscuity are probably factors in the increasing incidence of vaginitis in indigent patients. Large families and lack of household aids leave most of these women little time to worry about a condition which many of them regard as perfectly normal. The private patient, on the other hand, is not only generally more cognizant of bodily discharge as a sign of possible malignancy, but also has the leisure and means to indulge in the investigation and treatment of minor discomforts.

It is interesting to note that in his original study Dr. Gardner found an incidence of 12 per cent of *Haemophilus vaginalis* vaginitis in a group of 1,181 white private patients. With the addition of 1,070 similar patients, the incidence remains 12.2 per cent. In the same large group the per cent of moniliasis is 4.9. Since the authors do not make the diagnosis of moniliasis on incidental positive smears and cultures in the absence of gross or subjective evidence of the disease, I would like to ask Dr. Gardner what per cent of the patients with *Haemophilus vaginalis* vaginitis had subjective evidence of the disease.

Bacteriological culture of *Haemophilus vaginalis* is not, of course, a feasible method of diagnosis for the practicing gynecologist. Since such a diagnosis is based primarily on the presence of so-called "clue cells" in wet mounts, I would like to know whether Dr. Gardner has observed these cells in other types of vaginitis, and, if so, how they differ from those present with *Haemophilus vaginalis*. Since these cells are easily observed, any specific characteristics would be most important to recognize.

DR. LAMAN A. GRAY, Louisville, Ky.—I am wondering if there is such a thing as a nonspecific vaginitis. The more we study the cases, the more we find *Trichomonas* or something else. In Louisville we have tried intensively to culture this organism in 42 cases of vaginitis, and cannot cultivate it.

Two years ago Dr. Gardner stated that these patients need not have pus cells in the secretion or inflammation in the vaginal wall, and yet they would have vaginitis. I cannot understand how that could be vaginitis, and I wonder if he still feels that way.

DR. W. F. GUERRIERO, Dallas, Texas.—After we designate these individuals who have neither trichomoniasis nor moniliasis as "H.V.," our problem is what to do with them. We have been able to clear up "H.V." in the female, temporarily, but then we find these patients either getting reinfected or having recurrences.

We began to approach the problem from the male angle, as we did with trichomoniasis. We began to find the same thing—in approaching the male with *Trichomonas*—as we have in "H.V."

When we told the female that she must go home and tell her husband that he might have "H.V.," or that he might have trichomoniasis, or moniliasis, we found it difficult to get her to do so, for two reasons. First, she is a little bit hesitant to bring it out to her husband, because she realizes he might think he has some venereal disease, which will lead to a large amount of conversation. Second, if she does bring it up, and he knows a urologist, and he says, "You do not have it," he will come back home, and there will be more "pillow talk" as to "where did you get it?"



Third, we just do not have the time to spend with the husband to try to explain to him where he did get it.

What I want to know is just how to answer this problem.

DR. JOHN D. WEAVER, Austin, Texas.—After over 3,600 cases in the state institutions, we found that by culturing *Trichomonas*, we could often find it, but we were never able to grow it in the vagina of a woman who had normal tissue. We implanted in a number of cases, and we found that if we treated the organ instead of the organism, our results were excellent.

The paper that Dr. Gardner has presented brings up a question for me in the future that I am almost afraid to face. Here are 2,251 cases presented, and one case of gonorrhea. It was not so long ago in this organization—no longer than I have been a member, some 12 years—that many of our papers had to do with venereal disease. The problem that I am confronted with is this: soon my oldest son will go off to college, and I am wondering what I am going to tell him.

DR. GARDNER (Closing).—In answer to Dr. Zelle, we are of the opinion that *Candida* is part of the normal microbiological flora of the vagina, and it is commonly part of the normal flora of the intestinal tract, the oral cavity, and probably the ears and intertriginous areas of the body. Only under certain conditions favorable to its rapid multiplication does it become pathogenic. Definitely if there is an absence of subjective symptoms or gross findings of infection, we cannot classify the patients as having disease.

In regard to the per cent of patients with *H. vaginalis* vaginitis who had subjective symptoms, I must say that relatively few had itching or other symptoms of irritation, but the majority were conscious of an odorous discharge, but perhaps a patient's awareness of a discharge is objective rather than subjective.

In regard to Dr. Zelle's question about the diagnostic value of so-called "clue cells," we do acknowledge that other bacteria, such as diphtheroids, small cocci and *Vibrio* may cling to epithelial cells and produce a cell which can be confused with the typical "clue cell" of *H. vaginalis*. If a patient has a discharge similar to that of trichomoniasis, which yields typical "clue cells" and heavy fields of short gram-negative bacilli but no trichomonads, the diagnosis of *H. vaginalis* vaginitis is justified. Time does not permit detailed descriptions of typical and atypical "clue cells."

I cannot tell Dr. Gray why he has been unable to culture the organism. It is not expected that every laboratory will be immediately successful. We have repeatedly pointed out the technical difficulties in culturing *H. vaginalis*, and this is because of its fastidious nature. Dr. Gray also inquires as to why we classify the infection as vaginitis. The organism is a surface parasite which apparently thrives on vaginal secretions, but has no tendency to invade tissues. It is productive of a foul-smelling discharge which is definitely abnormal. The term "vaginitis" today has a rather broad interpretation. We are definitely dealing with disease and it is infection.

## Original Reports

### PROLAPSE OF THE UMBILICAL CORD\*

#### An Evaluation of Cord Prolapse as an Increasing Indication for Cesarean Section

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**I**N 1940, Mengert and Longwell<sup>1</sup> published an article on treatment of prolapse of the umbilical cord. They most adequately expressed the opinion of that time and for years to come when they stated, "Cesarean section was not generally used since it has not been considered justifiable to expose the mother to increased risk for a baby whose chances [of survival] are so poor."

In recent years, cesarean section mortality has been reduced to a level that would hardly have been believable in 1940.<sup>5</sup> This naturally has led to liberalization of the indications for the operation. Among these broadened indications, prolapse of the funis stands high in our institution.

#### Material

During the years 1951 to 1955, inclusive, there have been 19,893 term and premature deliveries at the Confederate Memorial Medical Center. Of these, 66 were complicated by prolapse of the umbilical cord. This is an incidence of 0.3 per cent, or one in every 302 deliveries. Twenty-five of these cases were treated by cesarean section and 5.8 per cent of all cesarean sections were done for treatment of prolapse of the umbilical cord. All of the cases included in this report were deliveries in which the fetus weighed 1,000 grams or more. There was no maternal mortality.

**Etiology.**—It is generally agreed that malpresentation is the most common etiological factor. Breech, transverse, compound, and face presentation occurred in 46 (60.7 per cent) cases. Over one-half of the malpresentations were breech presentations with footling breech most commonly noted (80 per cent). Abnormal placentation, as manifested by marginal placenta previa, was present in 6 per cent of the cases. Multiparity, with its tendency toward laxity of the uterus and abdominal musculature, has been implicated as a predisposing factor. The parity of 20 of our 66 patients was vi or more. Multiple gestation was noted in 6 (9 per cent) of the cases, with prolapsed cord occurring twice with the second twin. Prematurity was a complicating factor in 23 (34.8 per cent) of the cases. Of these, 14 were breech presentations. Polyhydramnios was present in one case.

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*Fetal Mortality.*—Since prolapse of the umbilical cord per se is not a cause of maternal mortality, we must keep that fact in mind in the management of these cases. Our first objective, then, is to classify these infants correctly as (1) salvageable and (2) nonsalvageable. The criteria used to determine salvageability are the presence of a pulsating cord and/or audible fetal heart tones in a pregnancy of at least 28 weeks' duration with uterine enlargement compatible with the estimated gestation period.

TABLE I. FETAL MORTALITY

	NO.	NO. FETAL DEATHS	% FETAL MORTALITY
Salvageable cases	54	9	16.7
Nonsalvageable cases	12	12	100.0
Total	66	21	31.8

Fetal mortality for the purpose of this paper includes stillbirths and all neonatal deaths through the first 28 days after delivery. Of the 9 fetal deaths in the salvageable cases, 8 were neonatal.

Gross fetal mortality figures reported usually fall between 30 and 49 per cent. Our gross fetal mortality was 31.8 per cent. In the 54 salvageable cases, our mortality was 16.7 per cent. It is difficult to make a comparison with other reported fetal mortality figures because of differences in tabulation in regard to prematurity and corrective factors.

*Prematurity.*—Prematurity is known to have an adverse influence on fetal survival in general. It seems that this unfavorable predilection would be enhanced by prolapse of the cord which would tend to jeopardize the fetus doubly. Of the 9 infants who died in the salvageable group, 6 were premature (between 1,000 and 2,500 grams). Although there is a limit to what the premature nursery can accomplish, unquestionably more and more of these prematures will survive. In this series, prematurity was present in 34.8 per cent (23) of the total cases.

The resultant fetal mortality of the salvageable premature fetuses was 30 per cent. When this is compared with the 8.8 per cent fetal mortality of the term salvageable fetuses, it is readily appreciated that prematurity exerts a heavy toll.

TABLE II. EFFECT OF PREMATURETY ON FETAL MORTALITY

	NO.	NO. OF FETAL DEATHS	% FETAL MORTALITY
<i>Prematures.</i> —			
Salvageable, cesarean section delivery	8	1	12.5
Salvageable, vaginal delivery	12	5	41.7
Nonsalvageable	3	3	100.0
Total	23	9	39.1
<i>Term.</i> —			
Salvageable, cesarean section delivery	17	2	11.8
Salvageable, vaginal delivery	17	1	5.9
Nonsalvageable	9	9	100.0
Total	43	12	27.9

*Cervical Dilatation.*—The importance of cervical dilatation has repeatedly been attested as being the most important single factor in prognosis of fetal mortality. Kush<sup>9</sup> stated that the over-all fetal mortality was 72 per cent if the cervix was incompletely dilated.

In general, incomplete cervical dilatation has been adjudged to have an adverse effect on fetal survival. Cope<sup>6</sup> achieved the enviable result of

only 2 fetal deaths in 42 cases of incomplete cervical dilatation treated by cesarean section. We obtained slightly better fetal survival rates in cases with incomplete cervical dilatation than when the cervix was completely dilated. We feel that this is largely attributable to the liberal use of cesarean section in patients with incomplete dilatation. In our series, there were 3 fetal deaths in 24 cases managed by cesarean section. It is obvious that in this institution the amount of cervical dilatation has been most important in determining the method of management. Cesarean section has been resorted to in 24 of 25 salvageable cases with incompletely dilated cervixes. There was only one delivered per vaginam in a salvageable case with incomplete dilatation. This occurred because the cervix dilated rapidly from 6 cm. to complete dilatation and delivery of the fetus in 21 minutes.

TABLE III. IMPACT OF CERVICAL DILATATION ON FETAL MORTALITY IN SALVAGEABLE CASES

	SALVAGEABLE			NO. FETAL DEATHS	% FETAL MORTALITY
	CESAREAN SECTION DELIVERY	VAGINAL DELIVERY	TOTAL		
Cervix completely dilated or nearly so	1	28	29	6	20.6
Cervix incompletely dilated	24	1	25	3	12.0

*Presentation.*—Presentation has been implicated as being a factor in fetal mortality. It seems that vertex presentation would produce the greatest degree of cord compression, thereby leading to fetal distress and ultimate fetal death without proper therapy. Our results certainly support this, as 13 of the 21 gross fetal deaths occurred in vertex presentations. One would expect the cord compression in breech presentation to be much less and to be virtually nil in transverse presentation. Since 6 of the salvageable infants in breech and transverse presentations were delivered vaginally and subsequently died neonatally, one can infer that the delivery was a causative or additive factor. In the traumatic deliveries there were 2 instances of extensive lacerations of the cervix.

TABLE IV. EFFECT OF PRESENTATION ON FETAL MORTALITY

	NO.	NO. DEATHS	NO. SALVAGEABLE DEATHS	% GROSS FETAL MORTALITY	% SALVAGEABLE* FETAL MORTALITY
Vertex	30	13	2	19.7	3.7
Foot breech	24	5	5	7.6	9.3
Frank breech	4	2	1	3.0	1.8
Transverse	5	1	1	1.5	1.8
Compound	2	0	0	0	0
Face	1	0	0	0	0
Total	66	21	9	31.8	16.6

\*Fifty-four infants were deemed salvageable.

*Station.*—Fenton and D'Esopo<sup>7</sup> have stated that there is a direct relationship between the station of the presenting part and fetal mortality.

In the 21 known salvageable cases in which the presenting part was unengaged, a fetal mortality of 14.3 per cent was obtained, as compared to 18.0 per cent in the cases with engagement. Twenty of these cases were managed by cesarean section.

As with the relation of fetal survival to amount of cervical dilatation, our results tend to indicate that the station of the presenting part is most



important in determining the proper management. At our institution, if the presenting part was unengaged and the fetus salvageable, cesarean section has been employed liberally.

TABLE V. RELATIONSHIP BETWEEN STATION AND FETAL MORTALITY

	NO.	NO. FETAL DEATHS	% FETAL MORTALITY	NO. SALVAGEABLE CASES	NO. FETAL DEATHS	% SALVAGEABLE FETAL DEATHS
Engaged	36	13	36.1	28	5	18.0
Unengaged	24	6	25.0	21	3	14.3
Unknown	6	2	33.3	5	1	20.0
Total	66	21	31.8	54	9	16.7

### Management

*Cesarean Section.*—We have resorted to cesarean section in 38 per cent of our total cases and in nearly one-half of our salvageable cases. This incidence of 38 per cent is more than three times as frequent as is usually reported. A fetal mortality of 12 per cent was achieved in cases managed by cesarean section. Almost all reports indicate lower fetal mortality in cases treated by cesarean section.

In patients who are to be managed by cesarean section, adjunctive measures are instituted while the operating theater is being readied. Oxygen via a nasal catheter or mask, Trendelenburg position, and elevation of the presenting part by a hand in the vagina have been employed in an attempt to prevent further fetal compromise. Eastman<sup>12</sup> has shown that the oxygen saturation of the newborn can be increased by administration of oxygen in the terminal phases of the second stage of labor. Obviously, Trendelenburg position and elevation of the presenting part by hand should tend to alleviate pressure on the cord and thereby remove the precipitating cause of fetal hypoxia. The efficacy of these adjunctive measures is best illustrated by noting that in this series, there was an average of 57 minutes from the time of diagnosis until the fetus was actually delivered at cesarean section.

*Vaginal Delivery.*—The acumen of the obstetrician may be taxed to the utmost in determining the feasibility of vaginal delivery in some salvageable cases. The fetal mortality was 21 per cent in the 29 salvageable cases delivered vaginally. If the fetus is salvageable and if the cervix is completely dilated or nearly so and if the presenting part is engaged, vaginal delivery should be attempted. Operative delivery, exclusive of low forceps, was resorted to in nearly half of the vaginal deliveries. Breech extraction was the most commonly performed operative delivery (11 cases with 3 neonatal deaths resulting). Version and extraction were used on one occasion and the fetus died neonatally. The dexterity of the obstetrician, coupled with able assistance in the delivery room, is all important to ensure a favorable outcome if vaginal operative delivery of any magnitude is to be undertaken.

An average of 15 minutes elapsed from the time of the prolapse of the cord until the fetus was delivered. This indicates that if prompt delivery could be anticipated and other factors permitted, vaginal delivery was attempted.

All patients who have a dead fetus should be delivered vaginally unless otherwise indicated.

### Comment

The changes that have occurred during recent years in the management of prolapse of the umbilical cord are almost entirely a result of the increased safety of cesarean section. This has removed the need for the potentially dangerous and usually unsuccessful procedures, such as use of the Voorhees

TABLE VI. INCIDENCE AND RESULTS OF CESAREAN SECTION AS TABULATED BY VARIOUS AUTHORS

	NO. CASES REPORTED	% GROSS FETAL MORTALITY	% SALVAGEABLE FETAL MORTALITY	NO. CESAREAN SECTIONS PERFORMED	NO. FETAL DEATHS IN CASES MANAGED BY CESAREAN SECTION	% OF TOTAL CASES MANAGED BY CESAREAN SECTION	% FETAL MORTALITY IN CESAREAN SECTION
Mengert, <sup>1</sup> 1940	58	46.6	Not listed	1	1	1.7	100.0
Bourgeois, <sup>2</sup> 1940	155	49.7	40.7	4	0	2.6	0
Morgan, <sup>4</sup> 1948	50	50.0	40.5	8	2	16.0	25.0
Fenton and D'Esopo, <sup>7</sup> 1951	216	37.5	28.9	7	0	3.5	.0
Cope, <sup>8</sup> 1951	350	53.4	27.9	42	2	12.0	4.8
Kush, <sup>9</sup> 1953	105	49.0	Not listed	9	1	8.5	12.0
Bryant, <sup>11</sup> 1954	Unknown	Unknown	Unknown	20	4	Unknown	20.0
Schultz, <sup>10</sup> 1955	85	40.0	24.6	2	0	2.6	0
Confederate Memorial Medical Center, 1955	66	31.8	16.7	25	3	38.0	12.0

bag, Braxton Hicks version, and many methods of cord reposition. Most of earlier reports have stressed the poor fetal outcome if the cord prolapsed through an unfavorable cervix. Now, the prognosis is just the opposite.

In the cases where the prolapse occurs late in labor with the cervix completely dilated or nearly so, the methods of management have changed very little. It is here where individual judgment is tested, for no rule of thumb can apply. There is still a place for Dührssen's incisions and internal version with extraction, but the operator must consider his own experience and ability, along with the general condition of the patient, the salvageability of the fetus, and the condition of the cervix and the pelvis. These are the cases where there is the greatest risk of losing both mother and baby. It must always be remembered that prolapse of the funis is not dangerous to the mother until it has been recognized by the obstetrician.

This series, like most others, makes very clear the potential danger of umbilical cord prolapse in the multiparous patient with an abnormal presentation. Footling breech presentation is the most common example of this danger. Moore and Steptoe<sup>3</sup> found prolapse of the cord caused 20 per cent of all fetal deaths in breech presentation and 53.33 per cent of the fetal deaths in footling presentation. The over-all incidence of prolapse of the cord in footling breech has been reported as 13.6 per cent. This reminds us of the importance of trying to keep the membranes intact in these cases. When there is rupture of membranes, immediate sterile vaginal examination should be performed in an attempt to make an early diagnosis of prolapse of the cord.

### Summary

1. A review of 66 cases of prolapse of the cord during the five-year period of 1951-1955 has been presented.
2. Abnormal presentation, especially footling breech, is the most common predisposing factor.
3. The amount of cervical dilatation and station of the presenting part are of prime importance in determining the method of management.
4. Cesarean section should strongly be considered if prompt delivery is not anticipated.
5. A fetal mortality of 12 per cent was achieved in 25 cases managed by cesarean section.
6. Adjunctive measures such as oxygen, Trendelenburg position, and manual displacement of the presenting part are of value in alleviating fetal hypoxia.

### References

1. Mengert, W. F., and Longwell, F. H.: *AM. J. OBST. & GYNEC.* 40: 79, 1940.
2. Bourgeois, G. A.: *AM. J. OBST. & GYNEC.* 41: 837, 1941.
3. Moore, W. T., and Steptoe, P. P., Jr.: *South. M. J.* 36: 295, 1943.
4. Morgan, J.: *Brit. M. J.* 2: 820, 1948.
5. Dieckmann, W. J., and Seski, A. G.: *Surg., Gynec. & Obst.* 90: 443, 1950.
6. Cope, E.: *J. Obst. & Gynaec. Brit. Emp.* 58: 259, 1951.
7. Fenton, A. N., and D'Esopo, D. A.: *AM. J. OBST. & GYNEC.* 62: 52, 1951.
8. Brandeberry, K. R., and Kistner, R. W.: *AM. J. OBST. & GYNEC.* 61: 356, 1951.
9. Kush, A. W.: *AM. J. OBST. & GYNEC.* 66: 182, 1953.
10. Schultz, J.: *Obst. & Gynec.* 6: 657, 1955.
11. Bryant, R. D.: *AM. J. OBST. & GYNEC.* 71: 614, 1955.
12. Eastman, Nicholson J.: Discussion of Romney, S. L., Reid, D. E., Metcalfe, J., and Barwell, C. S.: *AM. J. OBST. & GYNEC.* 70: 791, 1955.

**POSTABORTAL SEPSIS DUE TO CLOSTRIDIUM WELCHII  
SIMULATING TRAUMATIC PERFORATION OF  
THE UTERUS**

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**C**LOSTRIDIUM *welchii* infections in the postabortal or puerperal states are uncommon but probably not as rare as might be supposed from the cases on record. Puerperal gas gangrene has been known for hundreds of years but the first accurate description was by Dobbin<sup>4</sup> in 1897.

In 1905 Little<sup>12</sup> published a classic article on the disease with accurate case reports. Toombs and Michelson<sup>15</sup> in 1928 summarized the cases in the literature then totaling 45. More than half of the patients died within 4 days. Hill,<sup>9</sup> in 1936, published a report of 30 cases which occurred in the Women's Hospital in Melbourne, Australia. Sixty-three per cent of his patients died. He found that 1 per cent of septic abortions were *Clostridium welchii* infections, and that 84 cases had been recorded in the literature by that time. In a recent report of 6 cases from Bellevue Hospital in New York<sup>5</sup> the incidence was 1 in every 781 cases of abortion. However, at the Maternity Hospital in Santiago, Chile, between 1948 and 1952, 75 cases of *Clostridium welchii* infection were reported,<sup>13</sup> an incidence of 1 in 307 cases. The over-all mortality in this series was 73.3 per cent.

It is interesting that both Falls<sup>6</sup> and Bysshe<sup>3</sup> have found that from 4.5 to 5.9 per cent of normal pregnant women harbored *Clostridium welchii*. Butler<sup>2</sup> was able to demonstrate 640 strains of this organism varying in virulence. The toxins have been described as a hemolytic toxin, a necrotizing toxin, a neurotoxin, and a myotoxin. Different strains can vary in the amount of these different toxins and death can occur within twenty-four hours, if the neurotoxin affects the vital nerve centers. As first stated by Welch<sup>16</sup> and concurred in by numerous writers, the bacillus needs dead or damaged tissue to grow and produce clinical symptoms. Substantially all the cases have occurred after attempts to produce abortion, but it is conceivable that the infection could occur spontaneously in an incomplete abortion, in view of the finding of the bacillus of gas gangrene in the vaginas of antepartum women. Jones and associates<sup>11</sup> stated that this infection is probably always endogenous and may come from the vagina or from the gastrointestinal tract.

Bratton<sup>1</sup> in 1941 first noted anuria in septic abortion and attributed it to the crush syndrome. Gill,<sup>7</sup> in an article in 1951 on anuria following septic abortion, found that half of his cases were due to hemolytic anemia from *Clostridium welchii* infection.



Because of the frequent treatment of any infection with penicillin or other antibiotics, Douglas and co-workers<sup>5</sup> feel that probably in most cases postabortal anuria, had it been looked for before therapy, might be due to *Clostridium welchii* infections.

*Clinical Course of the Infection.*—This varies widely. Douglas, Carney, and Pellillo group the clinical forms as follows:

1. *Clostridium welchii* in the vagina with no clinical symptoms. Either the strain is nonpathogenic or conditions for growth have not been fulfilled.

2. Localized uterine infection causing endometritis of varying severity so that the uterus may become distended with gas (physometra) or emphysematous. There is usually exquisite uterine tenderness with prostration, and the outcome is usually fatal.

3. Pelvic and peritoneal spread. In this form there is parametrial and peritoneal spread, localized or generalized and with or without gas formation. This is a very grave condition and most patients die, but not enough cases with antibiotic therapy have been collected for it to be evaluated properly.

4. Blood stream infection:

a. Bacteremia. The organism cultured from blood but otherwise no clinical signs of septicemia, other than fever.

b. Septicemia. Blood stream infection accompanied by the dramatic effects of hemotoxin. A fulminating course is usually seen and when the patient survives the acute phase, severe anemia and anuria are serious complications. Since the organism is an obligatory anaerobe it does not survive for long periods in the blood, so that signs of severe septicemia may be present with a negative blood culture.

c. Metastatic gas gangrene, spread to other parts of the body, with or without signs of septicemia.

In severe postabortal infections due to *Clostridium welchii* a rather characteristic picture has been described. Twenty-four to forty-eight hours after manipulation there is the onset of fever and chills, often with nausea and vomiting and occasionally diarrhea. The patient seems alert, and the pulse is disproportionately high as compared with the fever and the blood pressure is lowered. The temperature may even be subnormal. In septicemia the urine becomes burgundy colored and the patient takes on a peculiar mahogany hue due to the blood hemolysis and some cyanosis due to vascular collapse. A profound anemia may develop in a short time. The patient in a few hours may go from circulatory collapse, to cardiac failure, to pulmonary edema and death.

The septicemia may so overshadow the local cause that the diagnosis may be obscure. Isham and Finch<sup>10</sup> recently reported a case in which the admitting diagnosis was hemolytic anemia of undetermined cause. They also did spectroscopic studies on the blood pigments. Hill had previously reported the pigments to be free hemoglobin and methemoglobin but Isham and Finch showed that it was not methemoglobin but methemalbumin that was the

heme protein responsible for the brown color of the plasma. They also confirmed the findings of Hadley and Ekroth<sup>8</sup> that spherocytosis and increased osmotic fragility are outstanding features in these cases and in one of Hadley and Ekroth's cases the finding of spherocytes in a routine blood count led to the discovery of a *Clostridium welchii* infection with subsequent recovery.

The rapid method of making the diagnosis is by direct smear from the vagina or cervix. Large gram-positive rods will be found. Culture under anaerobic conditions will of course rapidly cause wild fermentation and gas formation in a few hours.

**Principles of Treatment.**—Before the period of antibiotics, Hill outlined the treatment as follows: (1) removal of the focus of infection by curettage or hysterectomy in advanced cases, (2) specific serum therapy, (3) fluid administration—oral, intravenous, or transfusion, (4) administration of alkalis, (5) treatment of renal failure by forcing fluids.

Hill believed that with established renal failure the prognosis was hopeless. Ross<sup>14</sup> has demonstrated that penicillin is the drug of choice, because it is effective in ordinary dosage and the patient can tolerate very high levels. Jones confirmed this and recommended 2 million units daily.

The status of specific therapy with gas gangrene antitoxin is now in some doubt. Mahn and Dantuono in Chile give 200,000 International Units daily but in their series, if it was not started within 24 hours of the onset of the disease, it did not seem to affect the outcome significantly.

The artificial kidney will probably be of considerable value in the treatment of patients who survive long enough to recover from the severe toxins of the infection.

### Case Report

This 28-year-old white housewife was first seen on Feb. 2, 1956, because of spotting since her last menstrual period which was on Jan. 5, 1956. She had had a heavy flow on January 30 and brown spotting on January 31 and February 1 and 2. She stated that the period which had started on January 5 had been on time and perfectly normal, and all previous periods had been regular and normal. At no time did she complain of any pain. General physical examination was entirely negative. Pelvic examination showed a parous introitus with a slight amount of dark red discharge coming from the cervix which was clean. The uterus was slightly enlarged, and bulged particularly on the right side in a somewhat asymmetrical shape, but it was quite soft and both adnexa were clear. Pregnancy of approximately two months with threatened abortion was diagnosed and patient was advised to go to bed and rest and was to call if there were any increased bleeding or cramps.

At noon on February 4 the patient came to the Hospital, complaining of very severe pain for approximately 12 hours or more, and with profuse vaginal bleeding with clots. The hemoglobin was 7.2 Gm. per 100 c.c. Examination showed active bleeding from the uterus which was the size of a three months' pregnancy. The cervix was partially patent and there was considerable tenderness in the lower abdomen. It was decided to evacuate the uterus immediately because of the profuse bleeding, since we had been able to get 2 pints of blood promptly from the blood bank.

Under general anesthesia, the patient was catheterized. Coming from the bladder was practically pure blood. It had the identical appearance of the dirty bloody discharge from the cervix. The uterus was sounded and gas bubbled out of the uterine cavity.

Nothing more was done and the patient was prepared for a laparotomy, because it was felt that the uterus and probably the bladder and possibly the bowel had been perforated. This seemed to fit in with the excessive amount of pain the patient complained of, together with the fact that this severe pain had lasted for 12 or 14 hours before she sought medical aid.

The husband was questioned, and he stated that he had suspected that his wife had done something as she was afraid to have another child because she was Rh negative. This further confirmed our suspicion of a perforation, so the abdomen was entered by a midline incision. The pelvis seemed quite normal except for some congestion. No perforation could be found in the uterus or in the bowel. The bladder flap was dissected down to separate the cervix and the bladder to look for a perforation but none was found. This incision was repaired. The uterus was quite large, and an incision was made in the fundus. Gas came out of the uterine cavity. Necrotic placental tissue was also evacuated at this time and the entire uterus was cleaned out. These findings left us with the belated conclusion that she had a gas gangrene infection. During the operation the patient received 2 pints of matched blood. Her general condition throughout the operation was satisfactory although the blood pressure at the onset was 80/50. At the conclusion of the operation the blood pressure was 110/60. Pulse was 130 to 140. It was then reported from the laboratory that the blood had shown gross hemolysis in the original sample. The patient was immediately started on 500,000 units of potassium penicillin intramuscularly every 3 hours. A smear of the vaginal vault revealed gram-positive large rods, consistent with *Clostridium welchii*.

The operation was concluded at 3:10 and by 7:30 in the evening the hemoglobin was reported as being 5.6 Gm., or 38.8 per cent; the erythrocyte count was only 700,000 and the leukocyte count 23,450 with 40 stab forms, 48 segmented cells, 11 lymphocytes, and 1 monocyte. The hematocrit was 20 per cent.

There had been no urine excreted but, when the bladder was washed out, the wash fluid was stained a red-brown color. A hematoma was also developing in the incision. The sutures were removed and a few clots were removed but no definite bleeding points were found. A Penrose drain was placed in the incision and the incision was loosely resutured. There was no evidence of gas in the wound and no crepitation. The patient was very sick and during the night the rectal temperature rose from 100° F. at 4 P.M. to 105.2° by 9:00 P.M. She was started on gas gangrene antitoxin, 60,000 units intravenously and then 10,000 units intravenously every 4 hours.

During the night the patient gradually took on a very peculiar mahogany-colored hue. No urine was passed at all. She was given 2 more pints of blood during the night and by noon her general condition was much improved. She was much more alert, but there was still no urine being excreted. The temperature was now 99.4° F. rectally. The pulse was much stronger, 120 a minute. The blood pressure ranged from 70 to 80 systolic and 40 to 50 diastolic.

At this time she was given norepinephrine intravenously to try to raise the pressure to a higher level in the hope that it might help her to excrete urine. By 8:00 P.M. still no urine was being excreted. Her temperature was normal and pulse fair, but maintained only by the addition of norepinephrine.

On the morning of February 6, the patient's infection seemed to be under control but she was completely anuric. Attempts were then begun to find an artificial kidney for her. Blood chemical studies at this time showed a carbon dioxide combining power of 33.3 vol. per cent; chlorides 550 mg. per cent; creatinine 4.5 mg. per cent; potassium 5.8 meq. per cent; sodium 124.2 meq.; urea nitrogen 85 mg. per cent.

At the time of her transfer to the Cleveland Clinic, for artificial kidney, her general condition was poor. Her temperature was 100.4° F. rectally, pulse 100, respirations down to 12 and irregular, and there was a slight suggestion of edema.

She was received at the Cleveland Clinic in poor condition and was under the care of Dr. Willem Kolff. He stated that he had found the blood chemistry determinations

substantially as we reported them. She was given sodium acetate solution for the hyperkalemia. The patient was placed on the artificial kidney and during the night she showed considerable improvement; however, her breathing became very irregular and while a tracheotomy was being considered she died about 7:00 A.M. An autopsy was performed by Dr. S. R. Gerber, Coroner of Cuyahoga County, Cleveland, Ohio.

The following are the significant findings:

**Genitourinary System.**—The kidneys were markedly swollen, weighing 310 grams on the left and 320 grams on the right. The capsule was thin, intact, and stripped easily. The cortical surface was a dark red-brown color and homogeneous. On cut section, with the usual resistance, the cortex and medulla were demarcated, but the cortex maintained its dark red-brown color while the medulla was a deeper purple red. The mucosa of the pelvic ureters and bladder was intact. The bladder was found empty. The uterus was markedly enlarged, weighing 300 grams. There was a sutured vertical laceration 3 inches in length arising at the fundus and dipping down over the anterior surface. There was another transverse laceration 3 inches in length distributed across the anterior ligament between the bladder and the uterus. Smaller incisions  $\frac{3}{4}$  inch in length were seen bilaterally in the broad ligaments. In situ an abundance of blood clot and bloody fluid was found in the posterior pelvic fossa interposed between the uterus and large bowel. The right tube was moderately edematous and swollen as was its opposite member. The right ovary was represented primarily by a dark-red fire-ball clot which apparently had replaced most of the ovarian tissue. The left ovary was not particularly remarkable. The cervix was dilated and externally no evidence of trauma, marks of instrumentation, or bruising was noted. The vaginal wall was likewise free of evidence of instrumentation and bruising.

**Microscopic Description.**—**Kidney:** The lower nephrons were plugged by hemoglobin casts and showed "copper wire" linings. There was interstitial hemorrhage. **Uterus:** The myometrium was hypertrophied. There were necrosis and hemorrhage of the endometrium and thromboses in veins.

**Final Diagnoses.**—Septic endometritis and bilateral hemoglobinuric nephrosis. Self-induced abortion. Pregnancy of 8 to 10 weeks' duration.

### Comment

This then is a case of postabortal *Clostridium welchii* endometritis with early septicemia causing massive hemolysis with anuria, then collapse and death. The circumstances of seeing a substantially well pregnant patient less than 48 hours before admission, the history of severe cramps and blood clots for 12 to 14 hours before admission, the findings of a 47 per cent hemoglobin with substantially pure blood coming from the bladder and gas coming from the uterine cavity when probed led to the erroneous diagnosis of uterine perforation.

It is hoped that this case report will raise the index of suspicion of this disease so that unnecessary surgery need not be done. It is felt, however, that definitive treatment in this case was not delayed over two hours and that the infection was under control within 18 hours. The massive hemolysis, complete renal shutdown, and vascular collapse had progressed too far to be reversible, however.

### Summary

1. A case of postabortal *Clostridium welchii* infection erroneously diagnosed as traumatic perforation of the uterus is presented.



2. The diagnosis is most rapidly confirmed by direct gram-stained smear from the uterus or vagina.

3. Early treatment consists of evacuating necrotic tissue from the uterus and the administration of large doses of soluble penicillin.

4. Later treatment is concerned with maintaining the oxygen-carrying capacity of the blood, electrolyte homeostasis, and possibly the use of the artificial kidney.

#### References

1. Bratton, A. B.: *Lancet* 1: 345, 1941.
2. Butler, H. M.: *J. Obst. & Gynaec. Brit. Emp.* 50: 105, 1943.
3. Bysshe, S. M.: *AM. J. OBST. & GYNEC.* 35: 995, 1938.
4. Dobbin, S. W.: *Johns Hopkins Hosp. Bull.* 8: 24, 1897.
5. Douglas, G. W., Carney, B. H., and Pellillo, D.: *Surg., Gynec. & Obst.* 97: 490, 1953.
6. Falls, F. H.: *AM. J. OBST. & GYNEC.* 25: 280, 1933.
7. Gill, Robert C.: *M. J. Australia* 2: 45, 1951.
8. Hadley, G. G., and Ekroth, R. D.: *AM. J. OBST. & GYNEC.* 67: 691, 1954.
9. Hill, A. M.: *J. Obst. & Gynaec. Brit. Emp.* 43: 201, 1936.
10. Isham, R. L., and Finch, S. C.: *New England J. Med.* 254: 317, 1956.
11. Jones, C. P., et al.: *Obst. & Gynec.* 5: 365, 1955.
12. Little, H. M.: *Johns Hopkins Hosp. Bull.* 16: 136, 1905.
13. Mahn, H., Erna, and Dantuono, Louise M.: *AM. J. OBST. & GYNEC.* 70: 604, 1955.
14. Ross, R. W. N. L.: *J. Path. & Bact.* 58: 441, 1946.
15. Toombs, P. W., and Michelson, I. D.: *AM. J. OBST. & GYNEC.* 15: 379, 1928.
16. Welch, W. H.: *Johns Hopkins Hosp. Bull.* 11: 185, 1900.

## SURGICAL BLEEDING TENDENCIES OF PATIENTS WITH CHRONIC PELVIC INFLAMMATORY DISEASE\*†

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THE objective of this study was to determine whether or not patients with chronic pelvic inflammatory disease bleed more, during operation, than patients who do not have chronic pelvic inflammatory disease. Many surgeons have been heard to comment on how liberally a patient with chronic pelvic inflammatory disease bleeds, as the incision is made and the abdomen opened for exploration. This impression has been virtually accepted as a dictum by some, and only as a probability by others. Suffice it to say, that there is no unanimity of opinion.

Discussions with Dr. Steven Schwartz, hematologist at the Cook County Hospital, indicated that he also had given this problem some thought. Accordingly, it was decided that a series of determinations were to be made on two groups of women: (a) control studies on women without pelvic inflammatory disease, and (b) hematologic traits of women with chronic pelvic inflammatory disease. The bleeding status of these individuals was to be estimated by drawing blood samples for the following: (a) complete blood count; (b) platelet count; (c) bleeding time; (d) clotting time; (e) clot retraction; (f) prothrombin time; (g) sedimentation rate; (h) hematocrit; (i) Rumpel-Leeds test (capillary fragility); and (j) vitamin C level.

Our controls consisted of 10 medical technicians from the Cook County Hospital, who volunteered for this duty. They were selected because of normal menstrual cycles, nulliparity, and freedom from any pelvic inflammatory disease. None had ever been treated for any gynecologic difficulties.

The patients with chronic pelvic inflammatory disease were selected from the various gynecologic services of the County Hospital. Those who had asymptomatic fibromyomas of the uterus complicating the pelvic inflammatory disease were included in this series. The blood specimens were drawn and laboratory work was done by the same technician. The observations and clinical evaluation of *normal or excessive bleeding at operation* were made by us and our resident. No special measuring devices were used. The anesthesia was ether and nitrous oxide-oxygen or spinal. In an occasional instance cyclopropane or ethylene anesthesia was used. In these latter cases, it was not felt that that anesthesia made any difference in the amount of bleeding evaluated at operation. Thirty-five women were studied in the active series.

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### Clinical Observations

#### *I. The Control Group—10 Women.—*

The hematologic studies on this group of women were made at two intervals:

(1) during the mid (nonbleeding) phase of the period; and (2) during the first or second day of their active bleeding phase.

##### *Red-cell count:*

*Normal:* 4.5 to 5.5 million per cubic millimeter.

*Controls:* All within normal limits. No noteworthy difference between bleeding or nonbleeding phase.

##### *White-cell count:*

*Normal:* 5,000 to 10,000 cells per cubic millimeter.

*Controls:* eight showed *elevations* from one hundred to one thousand during the first day of bleeding. One showed an increase of 4,000 cells. There was usually an increase in the polynucleophils. In one instance the monocyte and lymphocyte types predominated in the rise in cells.

##### *Hemoglobin:*

*Normal:* 13.0 to 15.0 Gm., 85 to 100 per cent.

*Controls:* five were classified as having mild to moderate iron deficiency anemias, e.g., the midcycle hemoglobin in these patients was less than 80 per cent. Two are now receiving iron therapy. Seven out of 10 controls showed variable degrees of elevations in the hemoglobin determinations during the active bleeding phase, while 3 showed decreases. The increases averaged 2 to 3 per cent, while the decreases were of the same proportion, e.g., 71 to 73 per cent; 74 to 77 per cent.

##### *Platelet count:*

*Normal:* 250,000 to 300,000 (Fonio's indirect test).

*Controls:* Nine showed a drop in the platelet count during the active bleeding phase of the cycle, while one showed an increase. The drop varied from 60,000 to 200,000 platelets. The one rise measured 75,000 platelets.

##### *Bleeding time:*

*Normal:* 1 to 3 minutes (Duke).

*Controls:* Seven showed an increase in the bleeding time during the first day of bleeding; 2 showed a decrease, one did not vary noticeably. The increases averaged 1 minute and 30 seconds, with one increase up to 7 minutes and 44 seconds, e.g., 2 minutes, 16 seconds (midcycle) to 10 minutes, 0 seconds (bleeding). The two decreases averaged 1 minute and 35 seconds.

##### *Clotting time:*

*Normal:* 5 to 15 minutes (Lee-White).

*Controls:* Five showed increases in clotting time during the first day of menstrual bleeding, while 5 showed no noteworthy changes. The increases varied from 1 to 6 minutes.

##### *Clot retraction:*

*Normal:* 18 hours (Lee-White).

*Controls:* No difference was noted in either phase of the menstrual cycle.

##### *Prothrombin time:*

*Normal:* 12 to 15 seconds (Quick).

*Controls:* No noteworthy differences were observed in either phase of the menstrual cycle.

*Hematocrit:*

*Normal:* 40 to 42 mm. (Wintrobe).

*Controls:* There were no appreciable differences in either phase of the menstrual cycle.

*Sedimentation Rate:*

*Normal:* 10 to 15 mm. per hour (Wintrobe).

*Controls:* Six showed decreases of variable degree on the first bleeding day, while one showed an increase. Three did not show any changes. The decreases varied from 2 to 6 mm.

*Rumpel-Leeds (Capillary Fragility) Test:*

*Abnormal:* Ten or more petechiae with a 7 to 8 minute compression.

*Controls:* Eight were negative during both phases of the cycle, while two showed a trace of petechiae on the first day of bleeding.

*Vitamin C levels:*

Not determined in the control group.

Our results show a relative leukocytosis occurring on the first and second days of bleeding, with most of the increase being in the polynuclear cells. Seven out of 10 showed an elevation in the hemoglobin during the active bleeding phase of the cycle. This is a paradox. Since the menstrual period is usually associated with some fluid retention and hemodilution, one would expect more of a decrease in hemoglobin, much the same as seen during pregnancy.

The platelet count was lowered during the active bleeding phase in 9 of 10 controls. This is in accord with the findings of others.<sup>1, 2, 3</sup> Pfeiffer and Hoff<sup>1</sup> were the first to show that the platelet content of the blood falls during the menses; the lowest value being reached on the second day of menstruation, after which the level rises slowly to normal. Pohle<sup>2</sup> later stated that the platelet count is characterized by a slow progressive decrease during the 14 days prior to menstruation, in a few instances there being little or no cyclic change in the platelet count. Genell<sup>3</sup> believes that the postmenstrual rise is due to absorption of necrotic endometrium. The reason or the mechanism for this variability in platelet behavior, however, is not known. Hormonal factors apparently do not play a role since platelets have been known to increase after parturition, abortion, surgery, trauma, as well as menstruation.<sup>3</sup> Apparently any stress stimulus can create an increase in platelet formation, as part of the body defensive mechanism.

The bleeding time was increased in 7 of 10 women in the control group during the first day of menstrual flow. The upper limit of normal in the Duke procedure is 3 minutes. In 2 of the control group, the increase in bleeding time was up to 10 minutes in one, and up to 11 minutes and 30 seconds in the other. These women had a midcycle bleeding time of 2 minutes and 16 seconds, and 3 minutes and 42 seconds, respectively. No other unusual findings were noted in either patient at any other time. Pohle<sup>2</sup> has also indicated in his studies that "the bleeding time seemed to be slightly increased during the premenstrual period." The bleeding time apparently reaches its highest point during the second day of flow, after which it is slowly restored to normal.

The clotting time is apparently subject to less variation than the platelet count or bleeding time. Five out of 10 controls showed increases in the clotting time during the first day of menstrual bleeding, while in 5 there were no significant changes.

This increase or prolongation at menstruation was emphasized by Jagic and Hicks<sup>4</sup> in 1927, though no indication was made of the instances, if any, when no changes were observed. Evidently they felt that all women manifest an increase in clotting time during the premenstrual phase.



The control group failed to show any significant changes during either phase of the cycle in the red-cell count, clot-retraction time, prothrombin time, and hematocrit. One showed a "trace" or slightly positive Rumpel-Leeds test, and a second control had a 1 plus positive test on the first menstrual day. This is in contrast with the findings of Henning<sup>5</sup> who indicated that the Rumpel-Leeds test is invariably positive in the early bleeding phase of the cycle.

While some changes were noted in the sedimentation rates in 6 patients during the first day of bleeding, the difference was not noteworthy.

It should be emphasized that while these aforementioned variables occur, the actual blood levels usually remained within the limits of normal standards, whether the woman was menstruating or not.

## II. Active Series—35 Patients.—

A. *Patients with excessive bleeding, 12:* Twelve patients were classified as "bleeding excessively—or more than is usually encountered" in a patient being subjected to a laparotomy. Seven had fibromyomas of variable size complicating the chronic pelvic inflammatory disease. The greatest amount of bleeding, however, was encountered in patients in whom adnexal pathology surpassed the leiomyomatous changes.

The findings in Table I seem to indicate that there is no direct relationship between the amount of excessive bleeding and the hematologic traits of our patients. In only one instance was the platelet count found to be less than normal, and yet not sufficient to be considered as a dyscrasia (101,829 platelets per cubic millimeter). Two patients had an elevated bleeding time (4 minutes, 35 seconds to 5 minutes, 10 seconds), but these are of minor degree and not significant. One patient had a slightly elevated clotting time (16 minutes, 20 seconds) which certainly could not have influenced the patient's bleeding behavior. The 2 patients with the elevated bleeding time had normal platelet counts, and normal clotting time. The patient with the elevated clotting time had a normal platelet count, and a normal bleeding time.

TABLE I. LABORATORY FINDINGS IN 12 PATIENTS WITH EXCESSIVE BLEEDING

<i>Red blood count</i>		<i>Clot retraction</i>	
Normal	6	Normal (complete)	12
Lowered	6	<i>Prothrombin time</i>	
<i>White blood count</i>		Normal	12
Normal	8	<i>Sedimentation rate</i>	
Elevated	4	Normal	2
<i>Hemoglobin</i>		Elevated	10
Normal	6	Slightly	4
Lowered	6	Moderately	6
<i>Platelet count</i>		<i>Hematocrit</i>	
Normal	9	Normal	8
Elevated	2	Lowered	4
Lowered	1	<i>Rumpel-Leeds (fragility)</i>	
<i>Bleeding time</i>		Normal (negative)	12
Normal	10	<i>Vitamin C</i>	
Elevated	2	Normal	0
<i>Clotting time</i>		Lowered	9
Normal	11	Not detected	3
Elevated	1		

The capillary fragility tests (Rumpel-Leeds) were normal in every patient. The hematocrit, hemoglobin, and red-cell figures corroborated each other. Six of 12 patients had lowered hemoglobin levels. In 4 of them the hematocrit was also lowered. In the 2 patients in whom the hemoglobin was only slightly lowered, the hematocrit was within normal limits. With one exception, the leukocytosis encountered was of the mild type, e.g., 12,000 to 14,000 white cells per cubic millimeter. The one patient with marked leukocytosis (40,000 per cubic

millimeter) had large tuboovarian abscesses. These determinations were usually made on the day of admission, or a day later. All patients were placed on chemotherapeutic and/or antibiotic therapy anywhere from 24 hours to one week before operation, so that they were considered adequately prepared.

Four patients had slightly elevated sedimentation rates, while 6 were moderately higher (40 or more mm. per hour) than normal. The degree of pelvic involvement influenced the amount of elevation. Five of these 6 patients were the most profuse bleeders. All had fairly extensive adnexal lesions. These figures emphasize a fact that may be overlooked or forgotten in this day of antibiotics, namely, that "the sedimentation test is more useful than the temperature curve, pulse rate, or leukocytic count, in determining the presence or absence of active infection, as well as its virulence."<sup>6, 7</sup>

Ascorbic acid studies indicated that not a single patient had normal plasma amounts. Nine had abnormally low titratable levels, e.g., 0.1 to 0.5 mg. per 100 c.c. plasma, while 3 had absolutely no detectable vitamin C. Two patients with particularly excessive bleeding were found in the latter group. More about this aspect of the study will be considered in subsequent paragraphs.

TABLE II. LABORATORY FINDINGS IN 23 PATIENTS WITH NO EXCESSIVE BLEEDING

<i>Red blood count</i>		<i>Clot retraction</i>	
Normal	18	Normal (complete)	23
Lowered	5	<i>Prothrombin time</i>	
<i>White blood count</i>		Normal	23
Normal	17	<i>Sedimentation rate</i>	
Elevated	4	Normal	3
Lowered	2	Elevated	20
<i>Hemoglobin</i>		Slightly	12
Normal	18	Moderately	8
Lowered	5	<i>Hematocrit</i>	
<i>Platelet count</i>		Normal	19
Normal	15	Lowered	4
Elevated	7	<i>Rumpel-Leeds (fragility)</i>	
Lowered	1	Normal (negative)	23
<i>Bleeding time</i>		<i>Vitamin C</i>	
Normal	18	Normal	1
Prolonged	5	Lowered	11
<i>Clotting time</i>		Not detectable	5
Normal	22	Not determined	6
Prolonged	1		

*B. Patients with no excessive bleeding, 23:* In this group of 23 patients who were not considered to have bled in any excessive amount during operation, the hematologic findings are not unlike those noted in the previous group. Thus, 15 out of 23 patients had normal hemoglobin levels, while 8 had abnormally lower concentrations. Eighteen out of 23 had normal red-cell counts, and 5 had low counts. The hematocrit statistics again parallel those of the hemoglobin and red cells, e.g., 19 were normal and 4 were lowered.

The platelet count, bleeding time, clotting time, clot retraction, and prothrombin time were within normal limits, except for a few minor deviations. Thus, in 7 patients the platelet count was elevated from two to three times that of our control figures, e.g., from 631,484 to 987,444 as the highest reading. Discussion as to why these higher levels occur is speculative. It has long been known that hemorrhage causes an increase in the number of platelets, but these patients were not bleeding in any noteworthy amount or duration. It has been shown that postmenstrual (after the second day of flow) rises in the platelet count do occur, but usually not exceeding 60,000 to 80,000 per cubic millimeter.<sup>2</sup> There was no overt evidence of toxic absorption from any necrotic tissue. It is an accepted fact that plasma blood will show a platelet count that is at

least 15 per cent higher than capillary blood; but the determinations of our patients were all made from blood drawn specimens, and technically handled by the same personnel. It is well known that suppurative infections can cause thrombocytosis, an abnormally elevated thrombocytic count.<sup>8</sup> It is therefore not remiss to assume that in some instances chronic pelvic inflammatory disease without abscess formation will cause milder elevations in the platelet count.

It is to be noted that in this entire series of 35 patients, there were 7 patients (2 of the excessive bleeders, and 5 in the group without excessive bleeding) who presented prolonged bleeding times, e.g., varying from 6 minutes, 9 seconds to 13 minutes, 5 seconds. Abnormal prolongation of bleeding time may be due to decreased fibrinogen in hepatic disease.<sup>8</sup> It may also be due to a defective capillary contractility, in explanation of the paradox of a prolonged bleeding time with a normal coagulation time.<sup>9</sup> Proliferative tissue changes associated with pelvic inflammatory disease can readily explain the probability of a defective capillary contractility. It is also possible that a deficiency of thromboplastin in tissue fluids may be a factor.<sup>8</sup> Whether this deficiency is noted in patients with pelvic inflammatory disease we do not know.

The results of the sedimentation tests were similar to those reported for the group with excessive bleeding. The Rumpel-Leeds tests were negative in all instances. Ascorbic acid studies showed only one patient with normal plasma levels. Eleven had lower than normal concentrations; 5 had no detectable vitamin C; and in 6 patients no determinations were made. It becomes quite apparent that the average gynecologic patient at the Cook County Hospital has little or no ascorbic acid in her body. This finding was consistent in both groups. Clinically, therefore, this deficiency was not significant, though noteworthy. There was no evidence of subclinical scurvy in any patient. This is in accordance with the accepted teaching that in spite of the importance of vitamin C in the maintenance of proper nutrition, its deficiency does not appear to produce primary disturbances of protein, carbohydrate, fat, or mineral metabolism.<sup>8</sup> It must require considerable deletion of ascorbic acid over long periods of time before evidences of scurvy appear! Finally, there were no wound infections in any of these 35 patients so that adequate healing can occur despite the deprivations of vitamin C.

#### Comment

We believe these studies indicate that no significant changes occur in the hematologic traits of patients with chronic pelvic inflammatory disease, whether they bleed excessively at operation, or not. How, then, can this exaggerated bleeding that occurred in 12 out of 35 patients be accounted for? Disease entities that produce changes in the blood-clotting substances constitute one group of hemorrhagic diseases, while those that produce changes in the vascular endothelium constitute another group of so-called nonhemorrhagic diseases. Gradwohl<sup>10</sup> has written, "If the vascular endothelium suffers from malnutrition, some degree of scurvy or marasmus with normal blood pictures in the clotting constituents will result. Further, vascular injury may be produced by chronic infections (and chemical poisons) with resultant symptoms."

It is entirely possible that these factors may produce a partially recovered vascular status as the disease progresses to the chronic stage, or even a state of irreversible damage, so that the endothelial recovery is permanently impaired. In such patients the larger peripheral vessels would show negative capillary fragility tests, but the vessels of tissue close to the source of insult would show abnormal behavior.



There is also the possibility that with inflammatory stimulation there occurs in some patients a proliferation of endothelial tissue with subsequent formation of new vessels of small caliber in areas near the site of infection, e.g., in the abdominal wall and omentum. This concept we believe is in accordance with the teaching of Boyd<sup>11</sup> who stated that "if the irritant is intense [oviduct and ovary] the effect is degeneration and destruction. If it is mild [abdominal wall, omentum, e.g., areas remote from the stimulus] the effect is proliferation. At the center of the inflammatory areas the action of the irritant is severe, so that the degeneration predominates; at the periphery the action is mild, so that the tissue may be stimulated to proliferate." This reasoning could be applied to the pelvic and extrapelvic findings in 12 patients with excessive bleeding. By the same token, if the irritant is mild then the behavior of local as well as distal tissue is one of proliferation focally, and little or no response to stimulation distally. This concept could explain the findings in our 23 patients without excessive bleeding at operation.

### Summary and Conclusions

1. The object of this study was to determine whether or not patients with chronic pelvic inflammatory disease bleed more during operation than patients who do not have chronic pelvic inflammatory disease.
2. The project consisted of data obtained from two groups of women: (a) 10 controls, and (b) 35 patients from the Gynecologic Service known to have chronic pelvic inflammatory disease.
3. The results characterizing each group are herein presented.
4. While certain interesting variations are noted in the control group, the actual blood levels of the different tests usually remained within the limits of normal standards.
5. There is no apparent direct relationship between the amount of excessive bleeding and the hematologic traits of patients classified as "excessive bleeders."
6. The hematologic studies of patients categorized as not having excessive bleeding are not unlike those found in the so-called "excessive bleeders."
7. Impressions and speculations have been presented herein, to account for the findings noted in these patients.

### References

1. Pfeiffer, R., and Hoff: *Zentralbl. Gynäk.* 46: 1765, 1922.
2. Pohle, F. J.: *Am. J. M. Sc.* 197: 40, 1939.
3. Genell, S.: *J. Obst. & Gynaec. Brit. Emp.* 43: 1124, 1936.
4. Jagic, N., and Hicks, J.: In Halban, J., and Seitz, L.: *Biologie und Pathologie des Weibes*, Berlin, 1927, Urban & Schwarzenberg, vol. 5, pp. 419-420.
5. Henning, N.: *Deutsch. med. Wchnschr.* 50: supp. 2: 1078, 1924.
6. Baer, J. L., and Reis, R. A.: *AM. J. OBST. & GYNEC.* 10: 3, 1925.
7. Baer, J. L., and Reis, R. A.: *Am. J. Obst. & Gynec.* 5: 3, 1926.
8. Kolmer, J. A.: *Clinical Diagnosis by Laboratory Methods*, ed. 2, New York, 1941, Appleton-Century-Crofts, Inc.
9. McFarlane, R. G.: *Quart. J. Med.* 10: 25, 1941.
10. Gradwohl, R. B. H.: *Clinical Laboratory Methods and Diagnosis*, St. Louis, 1935, The C. V. Mosby Company, pp. 372-373.
11. Boyd, W.: *Text of Pathology*, ed. 6, Philadelphia, 1953, Lea & Febiger, p. 97.

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### Discussion

DR. STEVEN O. SCHWARTZ.—This is an extremely difficult problem to investigate even under the very best of circumstances, and the studies reported on were undertaken during a period of tremendous growth in every phase of the problem: hemostasis, coagulation mechanism, and advances in our understanding of platelets and platelet function.

The approach to this problem at best is complicated. The number of controls as well as the number of essential studies are virtually endless. A number of additional studies have been suggested which should be made and which probably will be done in the future. I should like to suggest further studies in the course of this discussion.

It seems apparent from the report of the essayists that no significant differences existed in the groups considered, i.e., in the group that had excessive bleeding and the group that did not have excessive bleeding. Was this real or apparent? I suppose we are all in accord that differences are simply not apparent because our present facilities are not sufficiently refined to disclose them. From the standpoint of practicality, the means used in this study were those available in the average hospital laboratory. These studies do not enable us to prognosticate with any degree of certainty which patients will bleed excessively and which patients will not; thus the study is incomplete.

There are, however, positive findings of interest. One is the confirmation given to the finding that there is a rather precipitous drop in platelets in patients who are beginning or are just over their menstrual periods. This drop is from 50 to 75 per cent. In some of these patients in whom the platelet drop is so marked, there is an accompanying elevation in bleeding time. This brings up the question of timing for surgical patients. What time in the menstrual cycle was selected for operation? The patient who is just beginning to menstruate or is menstruating seems to bleed more than the patient who is not menstruating. Incidentally, this should be true not only in gynecologic operations but in surgery of any type. Even though the platelet count may be lower than normal, it cannot be sufficiently low to present any clinical manifestations.

Another interesting point that was brought out in the paper was that during the period of active bleeding there is usually an increase rather than a decrease in hemoglobin notwithstanding the fact that there is a certain amount of hemodilution. This suggests that during this period, which is a period of stress, there may be some drawing on certain reservoirs, such as the spleen. It would be interesting to compare Caucasian patients with Negro patients, since it is known that the spleen of the female Negro is only about half as large as that of the Caucasian. If the spleen acts as a reservoir, the Negro patient should respond less than the Caucasian. It would be interesting to study the same phenomenon in patients who have for some reason or other undergone a splenectomy.

I do not know how much emphasis should be placed on variations in vitamin C level, because this is one of the most notoriously inaccurate tests; it depends on who is making the test, how long the blood was in the laboratory before it was assayed, and how long it was in the ward before it was sent to the laboratory. Certainly, the vitamin C level seems to have no relationship to the bleeding.

Refinement of methods is essential before evaluation of the problems can be dependable. Perhaps more important than any factor and perhaps as difficult a technical problem as any is the evaluation of the blood vessels. Biopsies and histologic criteria do not provide the answer. In the appraising of a problem in bleeding we are dealing with not only anatomic changes in the vessels, dilatations in the vessels, increase in the numbers of vessels, but also physiologic changes in the vessels themselves, including the contractility of the musculature and the integrity of the endothelium. So far, to the best of my knowledge, this evaluation has not been possible in surgically prepared or surgically treated patients. There seems no doubt that the increased vascularity accompanying any inflammation will definitely contribute to bleeding but this is not the whole answer. There has been little attention paid to this rather large area of speculation because the changes in individual patients are also extremely difficult to assay.

Still another important facet is the protein nutrition of the patient. Again, although there are several methods by which to assay this, we know that none is entirely satisfactory,

because serum protein will quantitatively fail to reflect the total protein nutrition of the body. It measures the circulating protein but reflects only in the roughest way the total protein reserves.

Another fascinating question is that of the qualitative change in the platelets. This is something about which virtually nothing was known when the essayist's studies were planned. We now know that qualitative evaluation of the platelets can give us a great deal of information heretofore unavailable. The qualitative behavior of the platelets depends on many components, at least two of which, the serotonin and clot-promoting functions, are of prime importance in a study of this kind and therefore would have to be done. It is interesting in this connection that there recently has been an article published showing that not only is there a quantitative drop in platelets before and just at the beginning of the menstrual cycle but that there is also a change in their qualitative behavior which suggests a change in their activity. Whether this is related to serotonin activity is not known. This could be studied.

Finally, there are still further suggestions that present themselves. In any future studies the platelets will have to be qualitatively assayed. The question will also have to be answered as to what happens to such patients when they are operated on in other than the pelvic areas. Is there an increase in the bleeding from operations on the chest, head, or upper part of the abdomen, or what not, in patients with chronic infections and in women around their menstrual cycle? Why is there both a fall in the number of platelets and an apparent quantitative change in platelets about the time of the menses? It would be interesting if general surgeons were to make a comparative study as to excessive bleeding in patients without pelvic disease but simply in relation to the menstrual cycle.

DR. M. J. KILEY.—During what year was this study at Cook County Hospital made? Were the essayists sure that these patients had an adequate diet? Did these patients have antibiotic therapy?

DR. KANTER (Closing).—All these patients had marked pelvic inflammatory disease in the first, second, or third repeat attacks. They were patients in whom the disease had been present a long period of time. You might call them subacute. We were not concerned with bleeding in the pelvis. We know there is always excessive bleeding in removal of inflammatory disease. We were interested only in the abdominal-wall bleeding, because the statement was made that patients who are menstruating and patients who have chronic pelvic inflammatory disease or any disease with chronicity have a greater tendency toward bleeding.

What we have in mind is a study of the endometrium in cases of bleeding in the presence of chronic infection. These chronic infections and mild infections constitute an extensive problem. These tests are very expensive. I think I am capable of telling whether the patient's abdominal wall is bleeding excessively. I admit it is not the most scientific way.

In answer to Dr. Kiley, these were done within the last year. You know what the diet is with the patients we have at the Cook County Hospital. They certainly do not have adequate diet.

## Case Reports, New Instruments and Methods

### UNUSUAL FINDINGS IN HERNIAL SACS

#### Two Case Reports

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**H**ERNIAL sacs do not belong to the type of specimen which will excite enthusiasm or great interest in a pathology department, and they are frequently disposed of in the most expeditious manner. The following two examples are cited because careful histological examination showed facts of diagnostic value.

**CASE 1.**—A specimen was received with the notation that it represented a hernial sac of a 29-year-old white woman.

*Gross Description.*—The specimen was an indurated piece of tissue, measuring 10 cm. in greatest diameter, which contained much fat and a few grayish-white nodules.

*Microscopic.*—The section shows a tissue which contains large clusters of decidual cells (Fig. 1).

*Diagnosis.*—Endometriosis in umbilical hernia showing decidual reaction.

The following history was then obtained from the referring surgeon: This 29-year-old woman, para ii, gravida iii, complained of painful postoperative hernia. She had had an operation for a ruptured appendix at the age of 7, and developed a hernia around the age of 10. She had been in good health. She had noticed that during the two preceding pregnancies the hernia had increased in size and had become extremely painful. She came to her physician again because of painful hernia. Examination showed a 7 inch curved right lower quadrant scar with a large hernia in the mid portion. This was repaired. The hernial sac measured about 2½ by 5 inches. The uterus was consistent with a four months' pregnancy. Both tubes and ovaries appeared normal. The hernia was repaired.

*Comment.*—This was the first time the physician was aware of the fact that the patient suffered from endometriosis.

**CASE 2.**—A specimen was received with the notation that it represented a hernial sac of a 48-year-old patient.

*Gross Description.*—The specimen consisted of an epidermis-covered piece of tissue from the umbilical region to which much fat tissue was attached. The specimen measured about 8 by 4 by 4 cm.

*Microscopic.*—The section showed a tumor. The tumor was composed of atypical glandular structures which were lined by high cuboidal epithelium frequently of the

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goblet type. The glandular structures varied in size, and lay loosely in a fibroconnective tissue stroma. Frequently, they contained oval basophilic bodies (so-called psammoma bodies) (Fig. 2).

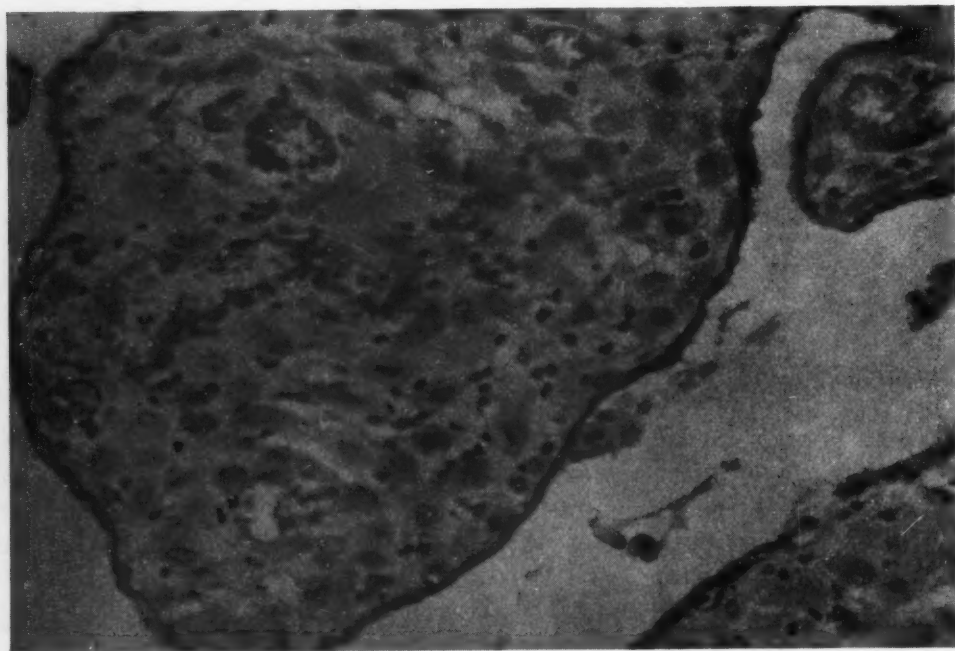


Fig. 1.—Case 1. Low-power photomicrograph of section from tissue in hernial sac showing decidua.

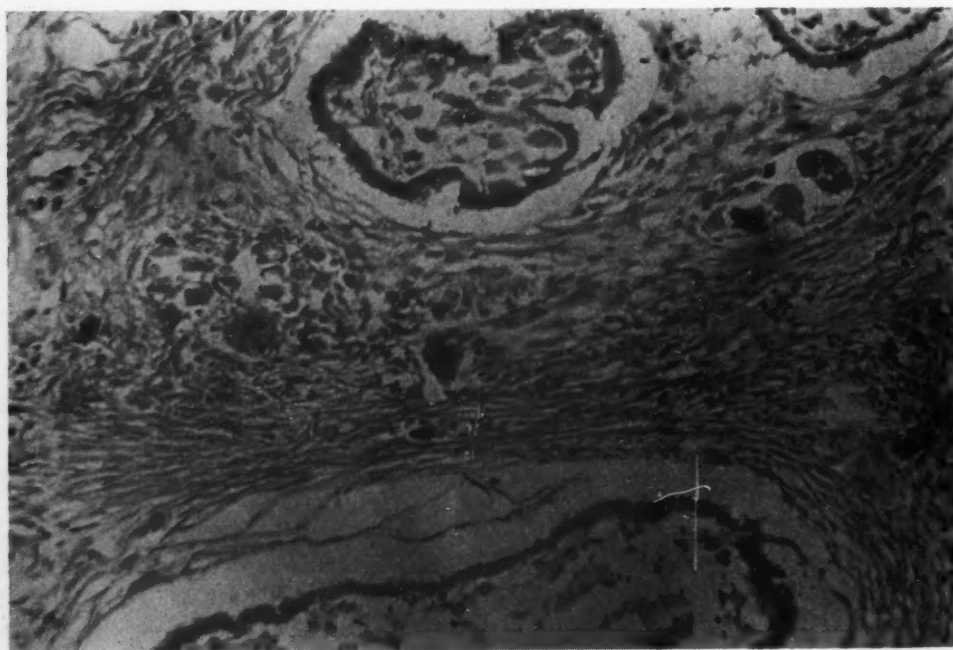


Fig. 2.—Case 2. Low-power photomicrograph of hernial sac, showing metastatic adenocarcinoma.



*Diagnosis.*—Hernial sac with metastatic adenocarcinoma. (In view of the psammona bodies, the tumor was probably ovarian in origin.)

Upon this report, an operation was performed. A small ovarian carcinoma was found which had the same histological appearance as the tumor in the hernial sac. No other metastases were found. The patient has survived for three years.

### Summary

Two cases are reported in which careful histological examination of a hernial sac permitted the establishment of a diagnosis of an important disease which otherwise would have gone unobserved.

## PSEUDOMUCINOUS CYSTADENOCARCINOMA OF THE OVARY IN A 19-YEAR-OLD PATIENT\*

### A Case Report

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**P**SEUDOMUCINOUS cystoma of the ovary is usually found in the fourth and fifth decades, but in the series of Cariker and Dockerty<sup>6</sup> the ages of the patients ranged from 10 to 80 years. An unfortunate omission in the reviewed literature is the failure to separate cases into benign and malignant types as related to age groups. Since malignant tumors are generally more prevalent in older age groups, it would be clinically and statistically significant to determine whether or not malignant and benign varieties of pseudomucinous cystomas occur with equal frequency in all age groups. The lack of emphasis on pseudomucinous cystadenocarcinomas occurring in the younger age groups is stressed in this case report of advanced bilateral pseudomucinous cystadenocarcinoma with metastases in a 19-year-old married woman who had never been pregnant.

Pseudomucinous cystomas make up approximately 15 per cent of all ovarian tumors, of which approximately 5 per cent undergo malignant change.<sup>3, 4, 7</sup> They are usually rapidly growing tumors and may reach enormous size. The largest appears to be that reported by Spohn<sup>3</sup> which weighed 378 pounds.

The teratomatous, Müllerian, and Wolffian theories of histogenesis were evaluated and reported by many authors, including Dockerty, Barzilai, Meyer and others. Histochemical studies have served to differentiate tumors which are morphologically equivocal into serous or pseudomucinous varieties, and have also served to clarify the nature of the mucin or mucinlike material. The morphological features of hyperchromatism, loss of cellular polarity, numerous mitotic figures, and cellular dedifferentiation are the criteria for malignancy in the cystadenocarcinomas. Many times only small localized areas of the cyst show malignant degeneration.

It is apparent from the accumulated literature on clinical behavior of the pseudomucinous cystadenoma that this tumor possesses a very bizarre and unpredictable clinical pattern. Weiner, Baumgarten, and Brandberg, as reported by Beecham,<sup>1</sup> described cases of histologically benign cystadenoma metastasizing along blood and lymph channels. Metastases to the spleen occurred 25 years after Brandberg removed bilateral pseudomucinous cystomas

\*The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval service at large.

which were histologically benign. It is believed that there were localized areas of malignancy which were not discovered even with numerous sections. Novak<sup>1</sup> discussed this possibility in a case reported by Beecham of a benign cystadenoma with malignant metastatic lesions to lymph nodes and vulva. The cases reviewed above indicate the possibility of malignant transformation of benign tumors and emphasize the importance of treating ovarian cysts in any age group with a high index of suspicion. The prognosis in benign cysts after operation is good. In cystadenocarcinoma the survival rate can be correlated in many cases with the grade and stage of the carcinoma found.

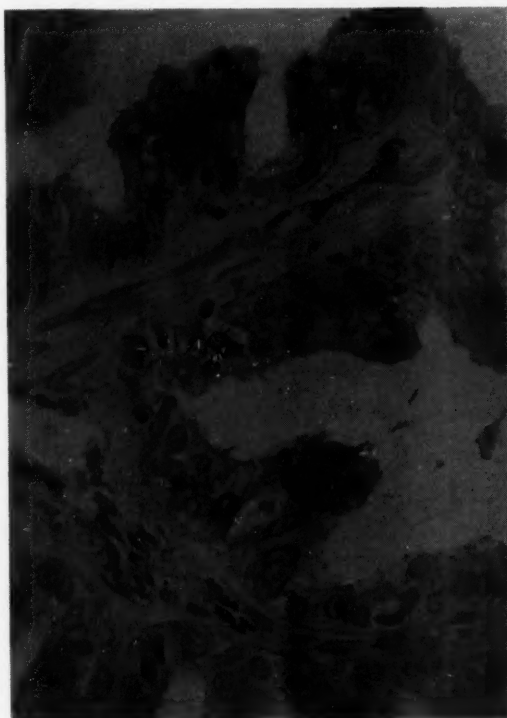


Fig. 1.



Fig. 2.

Fig. 1.—Pseudomucinous cystadenocarcinoma of ovary. There are moderate pleomorphism and hyperchromatism and one mitotic figure is seen in lower center.

Fig. 2.—Higher magnification of central area of Fig. 1, containing mitotic figure. Faint cell outlines and striking loss of polarity are seen.

This 19-year-old nulliparous white female was admitted to the U. S. Naval Hospital, Pensacola, Florida, on Oct. 31, 1955, complaining of a gradual increase in the size of the abdomen for the past 2 to 3 months. She thought she was pregnant, though her menstrual periods were regular, the last beginning Oct. 22, 1955.

For approximately three weeks prior to admission the patient had epigastric distress described as "heartburn" following meals. She also described vague lower abdominal discomfort, recent constipation, and pain on defecation. Despite enlargement of the abdomen she stated that she had lost six pounds during the last several months. On first examination the abdomen was noted to be distended and a fluid wave was elicited. Tenderness was present in the lower abdomen but no masses were palpable. The liver and spleen were not enlarged. Pelvic examination showed normal position of the cervix but the size of the uterus could not be determined. A normal-sized ovary was thought to be palpated on the right, and a tender, ill-defined mass was palpated in the left adnexal region.

Re-examination several days later, after the patient's symptoms had regressed somewhat, disclosed a lobulated mass in the pelvis extending to 4 cm. below the umbilicus. An irregular mass was also palpable in the right lower quadrant. Laboratory studies were within normal limits except for a corrected sedimentation rate of 42 mm. per hour. Tuberculin and Friedman tests were negative. Abdominal x-rays showed a soft-tissue mass approximately 14 cm. in diameter lying in the midpelvis.

At operation on Nov. 11, 1955, approximately 4 to 4½ L. of greenish, gelatinous fluid was found in the peritoneal cavity. There was a large, irregular, cystic tumor of the right ovary and a smaller cystic tumor of the left ovary. There was a large cyst in the cul-de-sac and there were numerous implants on the bowel, bladder, peritoneum, and liver.

During operation the fluid was evacuated from the peritoneal cavity, and a bilateral salpingo-oophorectomy was done.

The gross pathological examination included three specimens submitted and labeled separately. The first was labeled "Left Ovary," and consisted of an oval mass of tissue measuring 18 cm. in greatest diameter and weighing 1,250 grams. The specimen had a grayish-white, slick capsule which was perforated at one point by a 7 cm., fungating, cauliflower-like area which was slick, friable, and covered with a gelatinous material. The second portion was labeled "Portion of Left Tube," and consisted of a 5 cm. length of Fallopian tube. The third specimen was labeled "Right Ovary," and measured 8 by 5 by 4 cm. The capsule was smooth, gray, and glistening. The Fallopian tube was attached by fibrous adhesions.

Sections through the ovarian masses presented similar gross findings. Large cystic spaces containing a jellylike material were present. They were separated by septa of varying thicknesses. The walls of the cysts contained papillary masses of soft, friable tumor tissue which projected into the lumen.

Histologically, there were prolific papillary patterns which showed tall, pseudostratified columnar cells. The cells were arranged in frondlike patterns which radiated from a central stromal core. The nuclei were pleomorphic, hyperchromatic, and moderate numbers of mitotic figures were present (Figs. 1 and 2). Special stains carried out at the Armed Forces Institute of Pathology showed the secretion to be a mucin material, and the diagnosis was pseudomucinous cystadenocarcinoma of the ovary.

The patient made an uneventful postoperative recovery. On the tenth postoperative day, she was sent to U. S. Naval Hospital, Bethesda, Maryland, where she received colloidal gold for ascites and high voltage x-ray therapy. She is now being seen in our clinic at regular intervals with no evidence of recurrence to date.

### Summary

A case of bilateral pseudomucinous cystadenocarcinoma of the ovaries in a 19-year-old nulliparous white married woman is presented. A complete analysis of pseudomucinous cystomas, with separation into benign and malignant types according to age group was not encountered in the literature. It is felt that this is an unfortunate omission, and this case is presented in order to emphasize the unpredictable potentialities of pseudomucinous cystomas in younger age groups.

### References

1. Beecham, Clayton T.: *AM. J. OBST. & GYNEC.* 61: 755, 1951.
2. Weiner, S.: *AM. J. OBST. & GYNEC.* 69: 1015, 1914.
3. Novak, E.: *Textbook of Gynecology*, Baltimore, 1944, The Williams & Wilkins Company, pp. 412-414, 416.
4. Meyer, R.: *Monatschr. Geburtsh. u. Gynäk.* 44: 303, 1916.
5. Allan, M. S., and Hertig, A. T.: *AM. J. OBST. & GYNEC.* 58: 640, 1949.
6. Cariker, M., and Dockerty, H.: *Cancer* 7: 302, 1954.
7. Barzilai, G.: *Atlas of Ovarian Tumors*, New York, 1943, Grune & Stratton, Inc., pp. 161-237.



## MALIGNANT ARRHENOBLASTOMA OF THE OVARY

### A Case Report

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THE arrhenoblastoma has long been somewhat of an enigma to gynecologists and gynecological pathologists. One of the more puzzling features of the tumor is its degree of malignancy. Within the past several years the concept of arrhenoblastoma as having a much more malignant potential than heretofore considered has been brought forward and emphasized by notable gynecological investigators. It is the purpose of this report to emphasize this concept and to present a case with rapidly fatal termination in an 18-year-old girl.

This 18-year-old unmarried, white girl, B.C. No. 414629, was first seen on Aug. 30, 1954, by our medical department, complaining of abdominal soreness, of two months' duration, with aggravation during the last two days. This pain was apparently made worse by lying on one side or the other and just before or during urination or defecation. The menstrual history was considered normal to this point. She had undergone catamenia at 13 years of age with a fairly regular 28 to 30 day menstrual cycle with a 4 day flow. Her last menstrual period was two weeks before her appearance at this clinic. On examination, a striking, tender, firm, movable abdominal mass was palpated in the midline, which appeared to extend to within two fingers of the umbilicus. The internist who first saw this patient made a note of obvious hirsutism with a male pubic escutcheon. Gynecological consultation was immediately obtained and one of us (G. C. C.) made the initial examination. His note reads: "Marked hirsutism of arms, labia, and legs. External genitals normal. There is an intact hymen which barely admits a finger tip. Rectoabdominal examination reveals a solid, tender, irregular mass which fills the pelvis and extends to the region of two fingers below the umbilicus. The cervix and uterus appear to be small and displaced backward and to the left by the tumor mass. Impression: masculinizing tumor of the ovary."

The patient was admitted for study. Questioning at this time disclosed that, about two years prior to admission, the patient had experienced one day of severe abdominal cramping, which disappeared spontaneously. Also, at about this time, she noted a somewhat lengthened interval of time between what seemed to be normal menstrual periods (28 to 33 days). About two months prior to admission she noted some abdominal distention and fairly frequent bouts of lower abdominal pain and painful urination. It was actually the painful urination which brought her to the physician. On admission her temperature was 102.4° F. Urinalysis showed occasional leukocytes in clumps; no bacteria were noted and none could be cultured. Her leukocyte count was 14,700 with 77 per cent polymorphonuclears. The hematocrit was 34 per cent. An x-ray of the chest was negative. A study of 17 ketosteroids on a 24-hour specimen was reported as 11.4 mg.; a flat x-ray film of the abdomen showed only a hazy density in the lower abdomen without evidence of calcification. The patient was treated for the urinary tract infection, in preparation for operation.

On Sept. 8, 1954, an exploratory laparotomy was performed. A large, 10 or more inch in diameter, smooth-surfaced, nodular mass, which appeared to fill the pelvis, was immediately encountered. The omentum was adherent to the anterior-superior surface of the mass and contained several large blood vessels, some of which were as thick around as a lead pencil. The mass was easily delivered and it was noted to be the right ovary. The left ovary and uterus were apparently uninvolved. The right adnexa were removed intact with a large portion of the adherent omentum. The left ovary was bisected and no evidence of abnormality was noted. The pathologist was unable to afford a conclusive diagnosis on frozen section and because of the age of the patient and the fact that the capsule of this tumor appeared to be completely intact with no evidence of involvement of the opposite ovary, it was elected to close the incision and perform no further surgery.

The description of the gross specimen by the pathologist, Dr. Richard D. Bartholomew, is an interesting one: "The specimen consists of an egg-shaped mass, measuring 28 by 15 by 10 cm. Its surface is smooth, lobulated, and contains innumerable secondary small bosselations. The surface shows many large, tortuous blood vessels and pale gray-yellow areas, which might be calcification or fat necrosis. Cut surface reveals some homogeneous, rather translucent gray-yellow rubbery areas, but most of the tissue appears to be necrotic and in various stages, ranging from an early color change to a yellow-pink to purplish-red with much cyst formation, apparently due to necrotic tissue. Grossly, there did not appear to be any invasion of the capsule." The microscopic description was: "Numerous samples revealed fibrous tissue, diffusely infiltrated with rather large cells, with vesicular clear nuclei and pale staining cytoplasm. These cells in many areas tend to form large sheets and masses without forming any particular pattern. In these particular areas they tend to resemble a dysgerminoma, especially in some areas in which there is a heavy lymphocytic infiltration between them. In most of the sections, however, they form crudely outlined tubules, lined with cells which are slightly darker staining and smaller than the large pale cells. These cells lining the tubules appear to resemble Sertoli cells. Leydig cells were looked for, but were not found. The sections of the capsule in numerous places failed to reveal invasion throughout the entire thickness. Specimens are being sent to the California Tumor Registry and to Dr. Arthur Hertig for study. Diagnosis: probable arrhenoblastoma."

The postoperative course was uneventful with a speedy convalescence. The patient was discharged on Sept. 15, 1954. She was seen again on Sept. 28, 1954, and again on Oct. 19, 1954. A normal menstrual period had occurred on Oct. 7, 1954, lasting 4 days. Pelvic examination, done on her second visit on October 19, revealed nothing alarming.

One month later she had an episode of abdominal pain and vomiting, which lasted two days. A recheck on Jan. 21, 1955, showed that her menstrual periods were relatively normal, although she had noted some shortening of the interval between periods. A pelvic examination at this time was completely negative.

On Feb. 21, 1955, the patient presented herself because of abdominal distress and dysuria. Examination showed a distended abdomen, but no fluid wave. Tenderness was present throughout and bowel sounds were active. An irregular pelvic mass was now noted. Also noted at this time was a left supraclavicular nodule, on which a biopsy was performed in the outpatient department. The pathological report showed malignant invasion of a lymph node. The pelvic mass continued to grow and it was decided that another exploratory laparotomy should be performed, primarily for palliative reasons.

The findings at the time of the second laparotomy were discouraging. The entire pelvis was filled with metastatic tumor. The liver appeared to be smooth. Tissue was removed for pathological study and the abdomen closed. Postoperatively a bilateral small pleural effusion developed, which eventually resorbed without thoracentesis.

After presentation to the Tumor Board in April, deep roentgen therapy to the abdomen was begun. A tumor dose of 2,560 r was given in three weeks. In May, 1955, the patient was readmitted for x-ray therapy to the neck metastasis and for nitrogen mustard and corticosteroid therapy, as outlined by McCarthy.<sup>4</sup>

In June, 1955, a swollen, tender area was noted at the upper end of the abdominal incision. After hot compresses this spontaneously ruptured, releasing a large quantity of purulent material. The patient was readmitted.

Fig. 1.

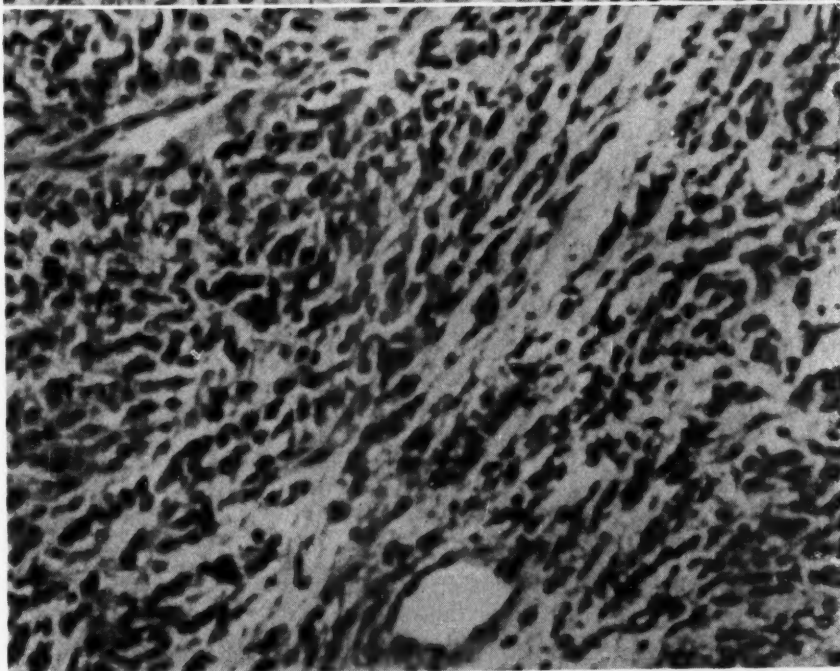
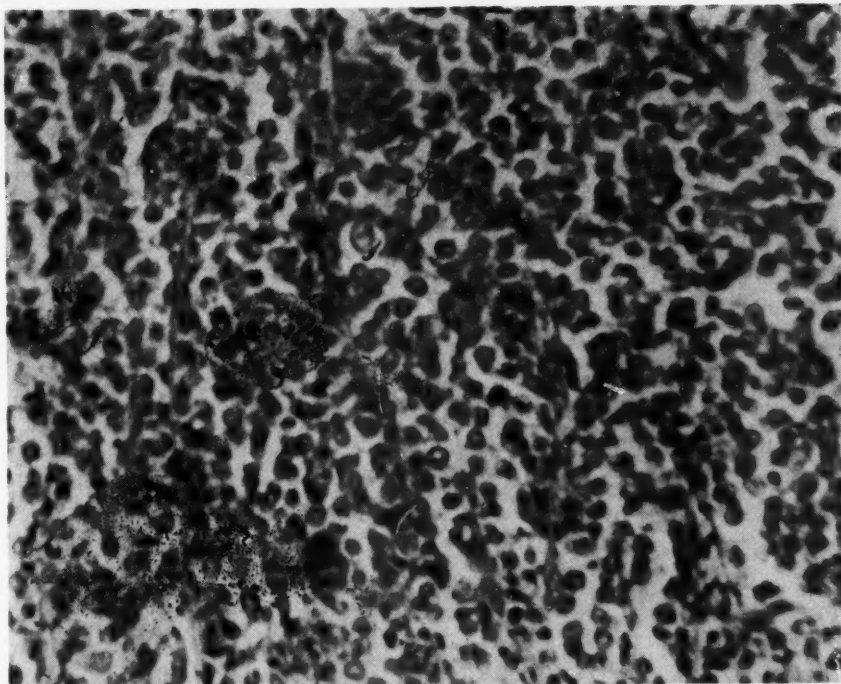


Fig. 2.

Fig. 1.—Microscopic section from original tumor.

Fig. 2.—Microscopic section from peritoneal implant removed at postmortem.



Chest films, bone films, and urinalyses at this time were negative. The leukocytes remained at between 18,000 and 20,000. During this hospital stay the patient was placed on intensive antibiotic therapy and a repeat course of intravenous nitrogen mustard was given. Improvement was slow but, as it was felt that she would be happier at home, she was allowed to go home on July 24, 1955. When she was seen as an outpatient one week later, it was obvious that her condition was deteriorating rapidly, and on Aug. 23, 1955, the patient died quietly at home.

A postmortem examination showed extensive metastatic disease with necrotic abscess cavities between the loops of bowel, extensive liver metastases, para-aortic, para-tracheal, and cervical node involvement.

### Comment

Javert and Finn<sup>3</sup> in 1950, in an excellent review of the subject, discussed the world's literature to 1949 and added several cases. They reported 27 malignant arrhenoblastoma out of 122 tumors. A search of the literature from then to the present yields 14 additional cases, none of which apparently displayed malignant tendencies.

The present-day division of the pathological types of arrhenoblastoma into (1) tubular adenoma; (2) intermediate; and (3) sarcomatoid type is a good working classification. It is difficult, however, to draw any hard and fast rules about therapy on the microscopic picture when gross malignant tendencies do appear, especially in the young age group. Javert and Finn stated that, in most cases, malignancy is evident at the time of the original operation and displays some or all of the following: ascites, adhesions, invasion of the capsule, bilaterality, weight loss, hydrothorax, and rapid growth. In general, they stated, if these criteria are not present, it is usually satisfactory in the young age group to perform a simple oophorectomy. If, however, "subsequent microscopic examination reveals an undifferentiated anaplastic-type tumor, the prudent action is to remove the remaining pelvic organs." It is especially with this last statement that we now wholeheartedly agree, although, in this particular case, it is hard to imagine any different outcome in the long run.

While pondering the exact course to take after the preliminary pathological report from the first operation, we were fortunate in having an opinion by Dr. Arthur Hertig, who stated "The best diagnosis I can make is a sarcomatoid arrhenoblastoma. This tumor has some pleomorphism and slight growth." The report from the California State Tumor Registry showed a unanimous diagnosis of arrhenoblastoma.

### Summary

A case of sarcomatoid arrhenoblastoma of the ovary is presented which, despite operation, irradiation, and nitrogen mustard therapy, progressed to a fatal ending. There was slight hirsutism but no elevation of the 17-ketosteroids, enlargement of the clitoris, or amenorrhea.

While the exact malignancy potential of the arrhenoblastoma is difficult to estimate, there are definite indications that it is higher than heretofore considered.



### References

1. Thomas, C. Y.: *Ann. Surg.* 135: 543, 1952.
2. Novak, E.: *Textbook of Gynecology*, ed. 4, Baltimore, 1952, Williams & Wilkins Company.
3. Javert, C. T., and Finn, W. F.: *Cancer* 4: 60, 1951.
4. McCarthy, W. D.: *New England J. Med.* 252: 467, 1955.
5. Flannery, W. E.: *AM. J. OBST. & GYNEC.* 60: 923, 1950.
6. Falk, H. C., and Mason, V. C.: *AM. J. OBST. & GYNEC.* 62: 1160, 1951.
7. Smiley, I., Beer, M., and Tandatnick, J. W.: *AM. J. OBST. & GYNEC.* 65: 208, 1953.
8. Wachs, C. S., and Weber, L. L.: *AM. J. OBST. & GYNEC.* 61: 212, 1951.
9. Hertig, A. T.: Personal communication, 1955.

2425 GEARY BOULEVARD

## LIPOLYMPH NODES: A REPORT OF THREE CASES

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**I**N THE past four years 3 cases of particular interest to us have been encountered at the Mayo Clinic. All 3 patients had greatly enlarged, benign pelvic lymph nodes at the time of pelvic laparotomy, and in one instance the large nodes produced a pelvic mass that prompted the laparotomy. In all 3 cases the pelvic lymph nodes had been almost completely replaced by adipose tissue and only a thin peripheral shell of lymphoid capsule remained. These nodes were called "lipolymph nodes."

The literature on this condition is scarce indeed; our search revealed reference to only one article published since 1916. King and MacCallum<sup>1</sup> in 1940 observed an apparent increase in the number of lymph nodes in regions that drained organs or tissues affected by inflammation or tumors. They examined tissue obtained by block dissection of the inguinal and axillary regions in cases of malignant disease and cite a few examples of glandular enlargement in the submaxillary, supraclavicular, mesenteric, and mediastinal regions. They reported masses of fat showing large numbers of lobules which varied in size from 1 mm. to 1 inch in diameter in the lymph node. All gradations from a fat lobule to a complete lymph node were observed; often the lymphoid tissue remained as only a rim around the periphery of the lobule. From their investigation King and MacCallum drew rather negative conclusions—they did not feel that their findings represented stages in the development of lymph nodes, nor did they strongly favor the possibility that fatty changes had actually occurred in the lymph nodes, though the latter surmise was regarded as a stronger possibility than the former.

The following reports concern the 3 patients whom we saw at the Mayo Clinic.

### Report of Cases

**CASE 1.**—A 49-year-old white woman, gravida v, para iv, registered at the Mayo Clinic in April, 1949. Ten years previously she had had a pelvic repair and had had a tumor of unknown nature removed from the cervix. The menopause had occurred at the age of 45 years. Results of cystoscopic examination performed because of intermittent dysuria and nocturia of several years' duration did not show any abnormality. She returned in December, 1950, with the same complaints. She was 64 inches tall and at this time weighed 171 pounds. Her blood pressure was 138 mm. of mercury systolic and 80 mm. diastolic. Results of the examination were otherwise negative except for thickening of both pelvic adnexal regions, especially the left, thought to be the result of an old inflammatory process.

\*The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Laboratory investigation revealed a concentration of hemoglobin of 13.2 Gm. per 100 c.c., a leukocyte count of 4,900 per cubic millimeter of blood, and a sedimentation rate of 17 mm. in the first hour. Urinalysis revealed pus, Grade 1; cultures of the urine were negative. The results of cystoscopic examination and examination of the colon were reported to be negative. Roentgenograms of the thorax did not show evidence of any abnormality. The patient was given a series of urethral dilatations and dismissed.

She returned to the clinic on March 29, 1951, complaining of intermittent suprapubic pain present since her last visit. The urinary symptoms had disappeared. Pelvic examination disclosed a vaguely outlined mass on the left side. The patient's obesity hindered examination but at this time surgical exploration was considered advisable. The patient, however, refused surgical intervention and again was dismissed. She returned to the clinic on July 18 of the same year still complaining of intermittent suprapubic pain.

Bilateral pelvic adnexal thickening was again palpable with a tender definite mass on the left, about 6 cm. in diameter.

On July 30 total abdominal hysterectomy with bilateral salpingo-oophorectomy was carried out. The uterus, tubes, and ovaries were atrophic. Large palpable masses, which varied from 5 by 4 by 6 cm. to 4 by 3 by 2 cm. in size, were found over both iliac arteries. Tumors, which appeared to be lipomas, were removed from regions adjacent to the right and left common and external iliac arteries.

The uterus weighed only 55 grams and contained atrophic endometrium. The tubes and ovaries also showed only senile changes. The masses proved to be lymph nodes with a prominent fatty component. The lymphoid tissue was confined to a thin rim around the individual nodes, the largest of which measured 7 by 5 by 3 cm.



Fig. 1.—Case 2. Two enlarged nodes.

CASE 2.—A 55-year-old white woman, gravida iii, para iii, had undergone her menopause at the age of 51 years. Her medical history was noncontributory. She was first seen at the Mayo Clinic on Aug. 1, 1951, with a history of postmenopausal bleeding of 3 months' duration. At the first sign of this bleeding she had consulted her home physician who performed a cervical biopsy which revealed a squamous-cell epithelioma. She had received 5,856 mg. hr. of radium therapy and she came to the Mayo Clinic for further consultation at the completion of her treatment.

The patient was 69 inches tall and weighed 210 pounds. Her blood pressure was 150 mm. of mercury systolic and 90 mm. diastolic. General physical examination showed only marked obesity.

On pelvic examination, an ulcerated, nodular lesion with a necrotic slough was found on the left side of the cervix near the external os. The fundus was mobile and felt to be of normal size. Slight thickening of the left parametrium was palpated. Cervical biopsies did not show any evidence of residual carcinoma.

Laboratory data showed a concentration of hemoglobin of 12.7 Gm. per 100 c.c., a leukocyte count of 4,000 per cubic millimeter of blood, 42 mg. of urea per 100 c.c. of blood, and a sedimentation rate of 29 mm. in the first hour. The urine was normal. She was given additional x-ray therapy to the pelvis through two portals anteriorly and two posteriorly and asked to return in 3 months.

She returned on Jan. 30, 1952, for consideration of a Wertheim hysterectomy and the operation was carried out on February 14. It was noted that the nodes in the right common iliac and both right and left external, internal, and obturator regions were enlarged to as much as 6 cm. in diameter and seemed to be replaced with fat. Evidence of residual or metastatic carcinoma was not found. Pathologically there was radionecrosis of the cervical canal and a fibroma 5 cm. in diameter arising from the right ovary. The most remarkable finding was the enlarged lymph nodes, which were similar to those mentioned in Case 1. The largest measured 6 by 3 by 3 cm. and showed fatty replacement with only a rim of lymphoid tissue remaining (Fig. 1).

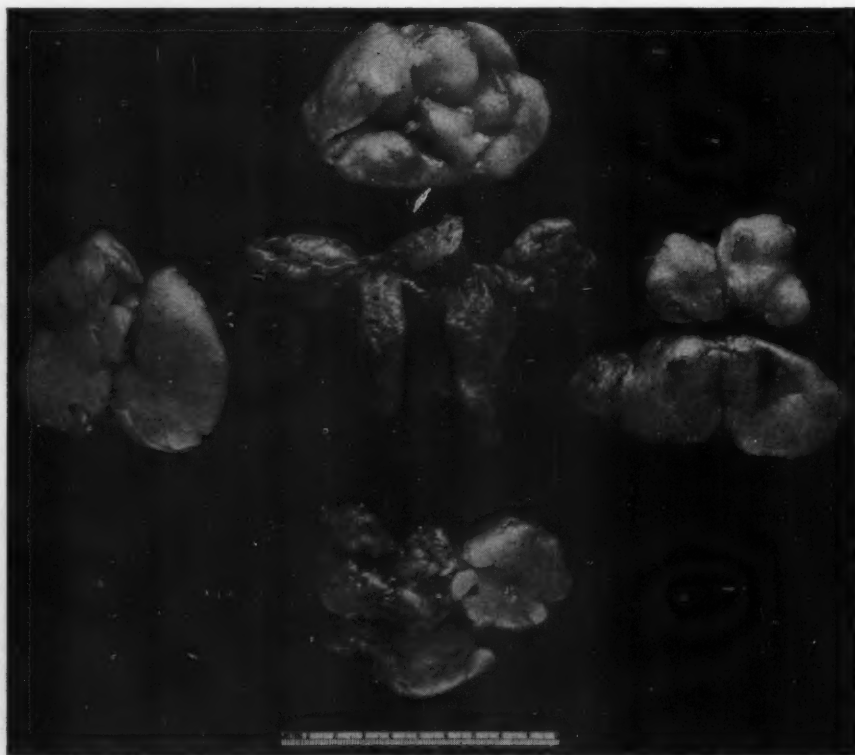


Fig. 2.—Case 3. Uterus, tubes, ovaries, and lipolymph nodes removed from pelvis of patient.

CASE 3.—A 57-year-old white woman, gravida vi, para vi, had experienced the menopause at the age of 54 years. She had undergone dilatation and curettage elsewhere in August, 1953, for postmenopausal spotting. No malignant lesion was found.

She was seen at the Mayo Clinic for the first time on Aug. 12, 1955. She had a history of heavy postcoital bleeding of a year's duration. She was 64 inches tall and weighed 212 pounds. Her blood pressure was 150 mm. of mercury systolic and 98 mm. diastolic. General physical examination revealed only the obesity and moderate varicosities of the lower extremities. On pelvic examination the cervix was clean and the uterus was found to be of normal size, but exhibited descensus, Grade 2. A cystocele and a rectocele, both of Grade 2, also were noted.



Laboratory data showed 11.7 Gm. of hemoglobin per 100 c.c. of blood and an erythrocyte count of 4.22 million and a leukocyte count of 5,000 per cubic millimeter of blood. Results of urinalysis were negative.

Fig. 3.

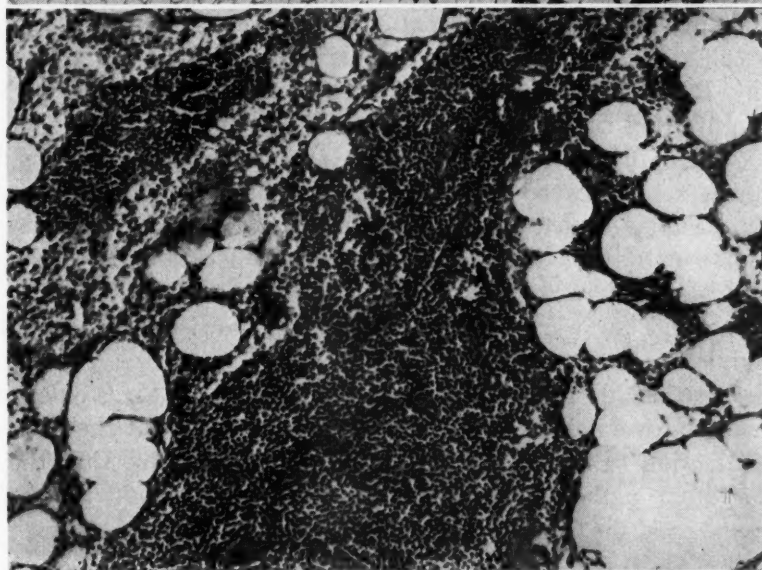
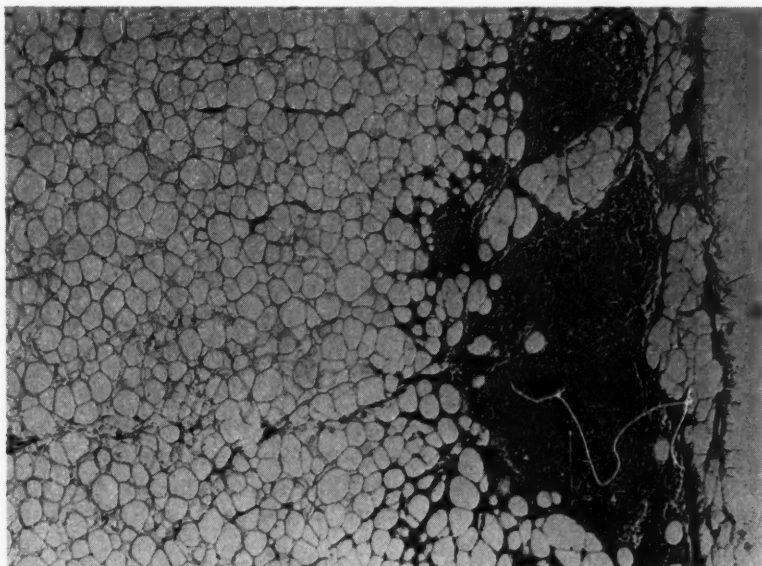


Fig. 4.

Fig. 3.—Case 3. Section of periphery of fatty mass showing inconspicuous lymphoid tissue margin. (Hematoxylin and eosin.  $\times 40$ .)

Fig. 4.—Case 3. Peripheral masses of lymphocytes and lymph node sinusoids evident in section of lipolymph node. (Hematoxylin and eosin.  $\times 100$ .)

A smear of cervical scrapings on Aug. 15, 1955, showed the presence of malignant cells. On August 29, conization of the cervix revealed an early infiltrative carcinoma of the cervix and Wertheim hysterectomy was then done. The right and left external iliac and obturator nodes were extremely large and seemed to have been replaced by fat, but they contained nothing suggestive of malignant disease. Aside from the microscopically

invasive squamous-cell carcinoma the only significant finding was the enlarged lymph nodes which measured up to 7 cm. in greatest diameter and were identical with those found in the other 2 cases (Figs. 2, 3 and 4).

#### Comment

All 3 patients who harbored these large benign lymph nodes were obese, weighing 171, 210, and 212 pounds, respectively. In case 1 repeated pelvic examinations prior to operation disclosed thickening of both adnexal regions high in the pelvis in spite of the patient's obesity. Exploration was advised to determine the nature of these masses, and, on inspection, the uterus, both tubes, and the ovaries were found to be atrophic. It seems reasonable to assume that the large masses of fat replacing the pelvic lymph nodes had been palpated and thought to be diseased adnexa. Perhaps more of these so-called lipolymph nodes would be found if laparotomy were performed on more obese women presenting rather indefinite pelvic findings.

It also is interesting and provocative of speculation that of these 3 patients one had had radium and x-ray therapy for a squamous-cell carcinoma of the cervix and a second was found to have an early invasive squamous-cell epithelioma on conization of the cervix. The third patient had had a so-called tumor removed from the cervix 12 years previous to laparotomy. However, in more than 350 Wertheim hysterectomies for carcinoma of the cervix these patients were the only ones noted to have large lymph nodes with fatty replacement and their association is probably coincidental.

The fat-replaced nodes in all 3 patients were very large, ranging from 4 to 7 cm. in greatest diameter. They were, therefore, much larger than the nodes described by King and MacCallum, though similar histologically. They are vastly different from the commonly observed fat-replaced "horseshoe" lymph nodes often found in the axilla which rarely measure over 1 cm. in diameter. As noted, these patients were all markedly overweight but had been so for some time. Therefore this unusual finding cannot be accounted for on the basis of recent deposits of adipose tissue. Except for the location the masses grossly resembled lipomas in having thin, smooth capsules readily freed from the surrounding tissues. They were soft, homogeneous, yellowish, and without definite palpable nodules.

Our observations do not elucidate the pathogenesis of these enlarged nodes. Their presence in overweight patients certainly suggests that the process is one of fatty infiltration. Because the nodes assume such a size that they can be mistaken for other pathologic conditions it seems they should be identified by name and we suggest the term "lipolymph nodes."

#### Summary and Conclusions

The cases of 3 patients having greatly enlarged, benign pelvic lymph nodes are presented. All 3 patients with this pathologic condition were obese.

In one patient the nodes produced clinically evident pelvic masses, and in the other two the masses were significant at the time of operation.

Because adipose tissue makes up the bulk of these nodes it seems appropriate to call them "lipolymph nodes."

#### Reference

1. King, E. S. J., and MacCallum, Peter: Australian and New Zealand J. Surg. 10: 126, 1940.

## HYDROCOLPOS AFTER TOTAL HYSTERECTOMY\*

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**H**YDROCOLPOS after panhysterectomy is so rare that no case was found described in the literature. We wish to report such a case and discuss the problems involved.

Case No. 56-760, Mrs. J. D., a 60-year-old para iii, gravida iv, office clerk, widowed for 30 years, was well preserved for her age.

At the age of 30 she was delivered of her last child by cesarean section, incidental to laparotomy for acute appendicitis with perforation. Bilateral tube ligation was carried out during this operation. She had some incisional drainage of unknown nature for about 6 weeks after the operation. Except for occasional upper respiratory infections and low backaches, she was in good health. Following the menopause, at the age of 51, she received Premarin intermittently for two years. In May, 1953, at the age of 53, she developed a vaginal discharge and irregular bloody spotting which lasted until October when abdominal panhysterectomy with bilateral salpingo-oophorectomy was performed. The diagnosis of the pathologist was endometriosis of the myometrium, cystic glandular hyperplasia of the endometrium, Nabothian cysts, and normal ovaries and tubes. Her postoperative course was uneventful, and she was well until November, 1954 (eighteen months later), when she began to complain of painless pressure in the lower abdomen, accompanied by a disturbing increasing frequency and urgency of urination.

Treatment was tempered by her work schedule and consisted of Terramycin, on the assumed diagnosis of cystitis. The volume of passed urine soon was reduced to a few teaspoonfuls at a time which, within a day, evolved into almost continual dribbling. She continued to work in spite of extreme discomfort. While sitting at her desk, she suddenly experienced "a bursting sensation inside," followed by the involuntary passage of a quantity of "urine," the flow of which continued until late evening. Following this incident, she became asymptomatic and urinated normal amounts five to six times a day without discomfort. She was first examined two weeks after the onset of symptoms and one week after reporting her symptoms by phone.

The abdomen was flat, without tenderness, pressure pain, or palpable masses. The patient passed clear urine and emptied the bladder without difficulty. The introitus admitted two fingers, but the vagina was no more than 1½ to 2 inches long, terminating in a conical segment. The vaginal mucosa was smooth and pale pinkish-yellow. The shortness of the vagina was ascribed to the cuff of the vaginal fornix removed with the portio vaginalis of the uterus. The patient was slender and of medium height, and evaluation of the pelvis by rectal examination was easy. With one finger in the rectum and a palpating hand over the thin abdominal wall, the empty urinary bladder was palpable without induration or abnormal pelvic masses. Again, it was assumed that the patient had had cystitis, which subsided under Terramycin medication. The significance of the "bursting sensation" and the subsequent passage of large amounts of "urine" was not understood, and it was assumed that the patient had overdramatized the incident. She was well during the following eight months, until Jan. 27, 1956, when she was hospitalized with acute urinary obstruction of approximately twenty-four hours' duration. The abdomen was markedly distended by a superficial symmetrical, ovoid mass extending from

\*Supported by funds from the Nelson M. Percy Research Foundation.

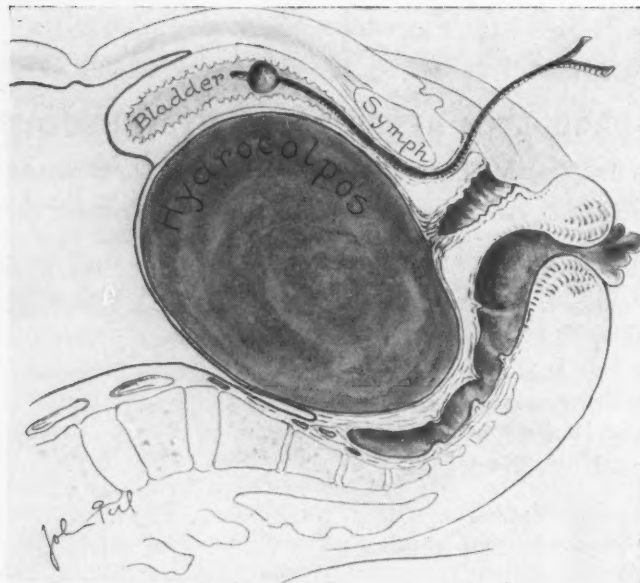


Fig. 1.—Topographical relations of the cyst.



Fig. 2.—Sections through the wall of the cyst showing its typically vaginal architecture.



the symphysis to the umbilicus, riding on a deeper lying, larger mass arising in the pelvis. The superficial mass proved to be the distended urinary bladder when it was reduced by catheterization of 750 c.c. of clear urine without altering its position, remaining palpable and visible up to the navel through the thin abdominal wall even after being emptied. The vagina was short, admitting about  $1\frac{1}{2}$  to 2 inches of the examining finger. The anus was edematous and ringed by huge protruding hemorrhoids. Rectal examination disclosed a large, fixed, elastic mass compressing the anterior rectal wall against the sacrococcygeal concavity with a force that made it difficult to advance the palpating finger beyond it.

A cystogram failed to demonstrate a communication between the urinary bladder and the pelvic mass. The bladder was kept empty with an indwelling Foley catheter, giving the patient a fair degree of relief and permitting the perianal edema to subside appreciably. At laparotomy, Jan. 28, 1956, a globular 20 cm. retroperitoneal cyst was found filling the pelvis, pushing the bladder neck against the symphysis, displacing the fundus of the bladder almost to the level of the umbilicus, and bound to loops of bowel by string-like and membranous adhesions. The ureters were identified above the posterior convexity of the mass and were greatly dilated. In spite of its large size and its almost symmetrically central position in the pelvis, the mass was assumed to be an intraligamentous cyst (Fig. 1). A "T" shaped incision was made through the peritoneal covering of the mass, and its lateral and posterior attachments were gradually freed by blunt and sharp dissection. The urinary bladder was inadvertently entered during this dissection, and after its interior was examined the tear was closed with two rows of catgut sutures. The cyst was ruptured during subsequent dissection, and its opalescent watery contents were aspirated. The cyst wall was excised except for a 3 cm. circular patch at the level of the trigonum. Considerable venous bleeding and oozing were controlled with ligatures and warm pressure packs. The peritoneum was sutured and the abdominal incision was closed without drainage. Her convalescence was complicated by an acute attack of glaucoma of the left eye, probably provoked by administration of atropine with the preoperative sedation and quickly controlled with myotics. The urine was blood tinged for a few days; the daily output was satisfactory. On the seventh postoperative day the Foley catheter was removed. The urine was normal except for catheterization debris. The cyst wall proved to be of vaginal origin on histological examination (Fig. 2).

### Comment

A cyst might be derived from the vagina as a result of maldevelopment or as a result of sequestration later in life. An embryonic origin can be excluded in the present case in view of the absence of the cyst at the time of two previous laparotomies and its position at the apex of the vagina, which would have interposed it between the lower segment of the vagina and the uterus, a location which would have interfered with the normal delivery of two of her three children. On the other hand, several incidents in this patient's history might have resulted in sequestration of the blind end of the vagina following hysterectomy. These include the stricture and the inflammatory changes incidental to senile vaginitis, and the trauma to which the vaginal epithelium was subjected in the preparatory scrubbing for surgery, and by the iodoform pack placed in it incidental to hysterectomy and removed from below postoperatively.

A more difficult question to answer is the source of the fluid in the cyst. The cyst developed over an eighteen-month period following a bilateral salpingo-oophorectomy and panhysterectomy. It is known that the cervical glands were completely removed. The possibility of the presence of ectopic

glands in the vaginal wall was ruled out with reasonable certainty by the fact that none were found in the multiple sections of the cyst wall studied microscopically. This leaves only the squamous epithelial surfaces of the vagina responsible for the opalescent watery contents of the cyst, which was under considerable pressure as attested to by the fact that the cyst apparently ruptured spontaneously in November, 1954, on the occasion of the episode of bursting and flooding, and after refilling over an eight-month period compressed the bladder to the point of complete obstruction to the bladder outlet. It also caused dilatation of the ureters, and markedly compressed the rectum and deep pelvic veins. The assumption that the vaginal wall, devoid of glands, was the source of the fluid is not unreasonable, since the vagina usually remains moist after total panhysterectomy. Whether or not estrogen therapy, by its effect on the vaginal epithelium, enhanced the formation of this fluid in the present case can only be conjectured.

#### Summary

1. A hydrocolpos developed to the point of causing obstruction of the bladder neck eighteen months after panhysterectomy, ruptured spontaneously through the vagina, and refilled during the following eight months.

2. Its pathogenesis is considered to be sequestration of a segment of vagina as the result of senile vaginitis and trauma incidental to surgery.

3. The cyst fluid was under considerable pressure and must have arisen as a transudate through the vaginal wall forming the cyst, or it might have been the product of ectopic glands which were not demonstrated histologically.

## MONOAMNIOTIC TWIN PREGNANCY

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THE occurrence of monamniotic twinning is relatively rare. In a review of 332 twins at the Chicago Lying-in Hospital from 1931 to 1941, Potter and Crunden<sup>1</sup> found no case of monoamniotic twins. King,<sup>2</sup> however, reported 5 cases in an 18 month period in New Orleans. This seems to indicate that the incidence of monoamniotic twins is greater than is generally believed and that many cases are not recognized as such and are therefore not reported.

The clinical diagnosis of monoamniotic twin pregnancy is impossible until the time of delivery. After delivery of the first twin, if there is prolapse of a twisted or knotted umbilical cord or if there is absence of the second amniotic sac, monoamniotic twins should be suspected. Immediate delivery of the second twin should be accomplished to prevent the effects of hypoxia resulting from tightening of the knotted cords.

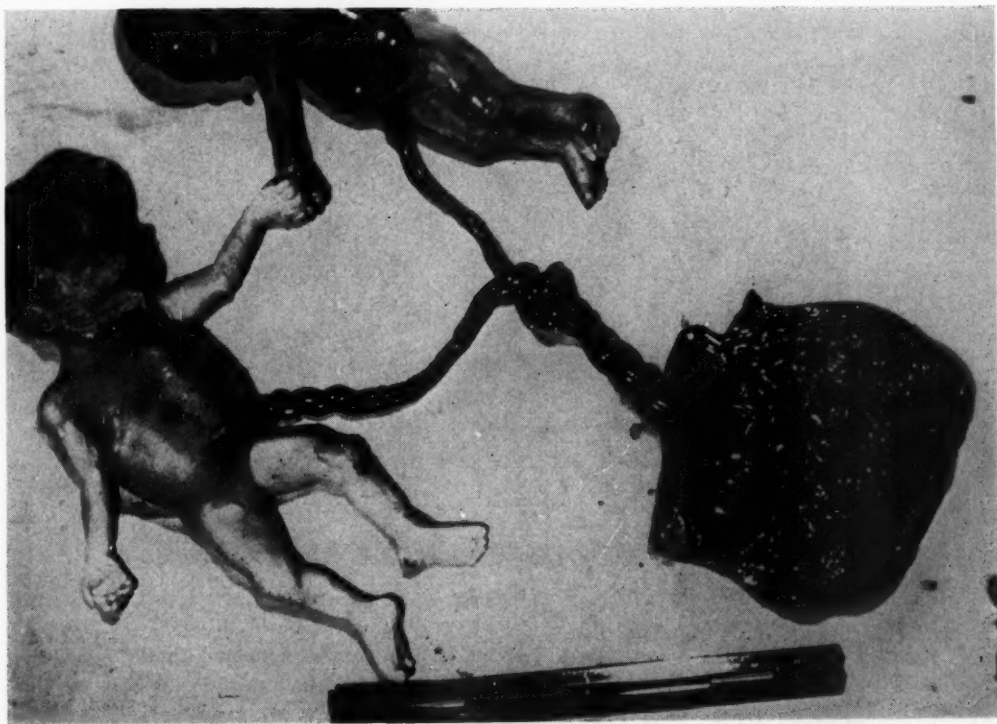


Fig. 1.

glands in the vaginal wall was ruled out with reasonable certainty by the fact that none were found in the multiple sections of the cyst wall studied microscopically. This leaves only the squamous epithelial surfaces of the vagina responsible for the opalescent watery contents of the cyst, which was under considerable pressure as attested to by the fact that the cyst apparently ruptured spontaneously in November, 1954, on the occasion of the episode of bursting and flooding, and after refilling over an eight-month period compressed the bladder to the point of complete obstruction to the bladder outlet. It also caused dilatation of the ureters, and markedly compressed the rectum and deep pelvic veins. The assumption that the vaginal wall, devoid of glands, was the source of the fluid is not unreasonable, since the vagina usually remains moist after total panhysterectomy. Whether or not estrogen therapy, by its effect on the vaginal epithelium, enhanced the formation of this fluid in the present case can only be conjectured.

### Summary

1. A hydrocolpos developed to the point of causing obstruction of the bladder neck eighteen months after panhysterectomy, ruptured spontaneously through the vagina, and refilled during the following eight months.

2. Its pathogenesis is considered to be sequestration of a segment of vagina as the result of senile vaginitis and trauma incidental to surgery.

3. The cyst fluid was under considerable pressure and must have arisen as a transudate through the vaginal wall forming the cyst, or it might have been the product of ectopic glands which were not demonstrated histologically.



## MONOAMNIOTIC TWIN PREGNANCY

DONALD WALTERS, M.D., AND DONALD WHITEHEAD, M.D., WASHINGTON, D. C.

*(From the Department of Obstetrics and Gynecology, the George Washington University and Hospital)*

THE occurrence of monamniotic twinning is relatively rare. In a review of 332 twins at the Chicago Lying-in Hospital from 1931 to 1941, Potter and Crunden<sup>1</sup> found no case of monoamniotic twins. King,<sup>2</sup> however, reported 5 cases in an 18 month period in New Orleans. This seems to indicate that the incidence of monoamniotic twins is greater than is generally believed and that many cases are not recognized as such and are therefore not reported.

The clinical diagnosis of monoamniotic twin pregnancy is impossible until the time of delivery. After delivery of the first twin, if there is prolapse of a twisted or knotted umbilical cord or if there is absence of the second amniotic sac, monoamniotic twins should be suspected. Immediate delivery of the second twin should be accomplished to prevent the effects of hypoxia resulting from tightening of the knotted cords.

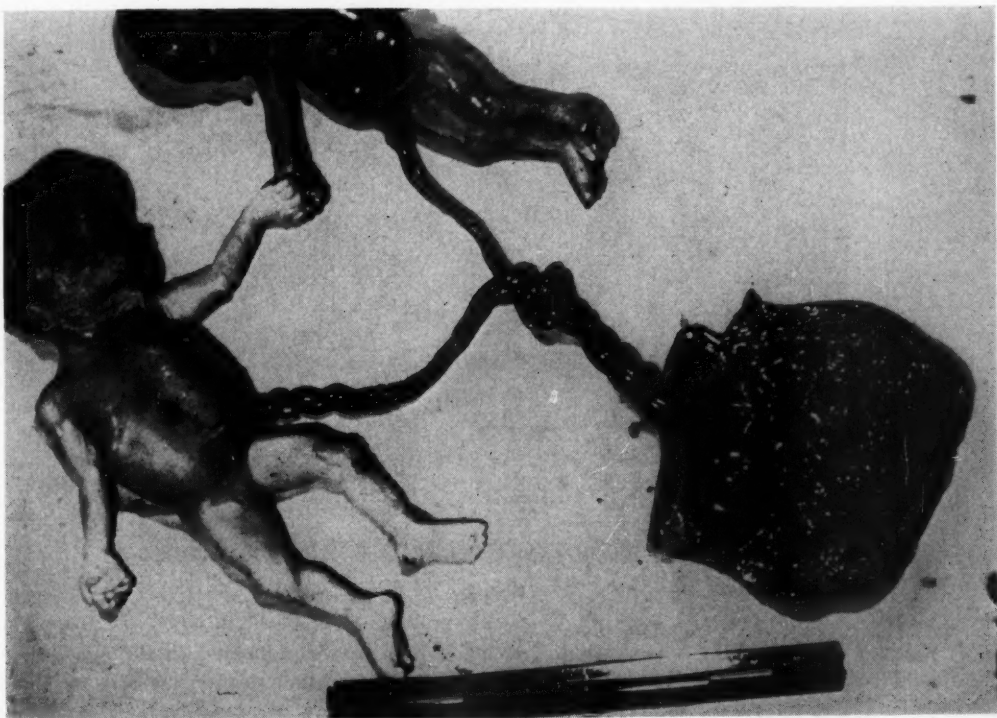


Fig. 1.

CASE 1.—Mrs. H. P., a 32-year-old gravida iii, para ii, went into labor on Sept. 12, 1955, six weeks prematurely. The diagnosis of twins was made in labor. Caudal anesthesia was used. When the cervix was fully dilated a compound left bregma anterior and arm presentation of the first twin was found. The second fetal head was impacted in the pelvis close beside the first head. The second fetal head and arm were dislodged with considerable difficulty. The first fetus was then delivered by midforceps. It was a viable baby girl who weighed 3 pounds, 12 ounces. The second fetus was then delivered spontaneously and immediately from a left mentum anterior position. The second twin weighed 3 pounds, 8 ounces. Both umbilical cords were found to be arising from the placenta 4 cm. apart with no evidence of a partition between them. They were tightly entwined and a true knot was present (Fig. 1).

The babies responded well to mild oxygen resuscitation, and were sent to the premature nursery in good condition. They have continued to progress well up to the present time (Fig. 2).

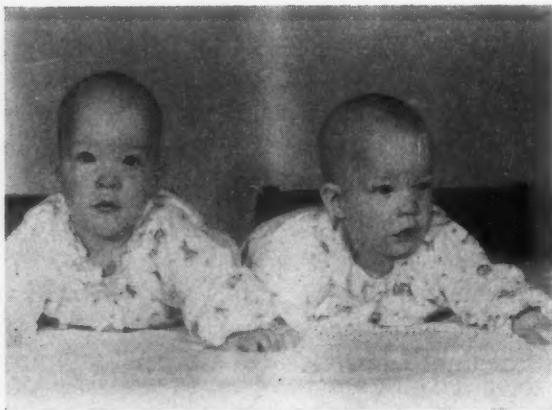


Fig. 2.

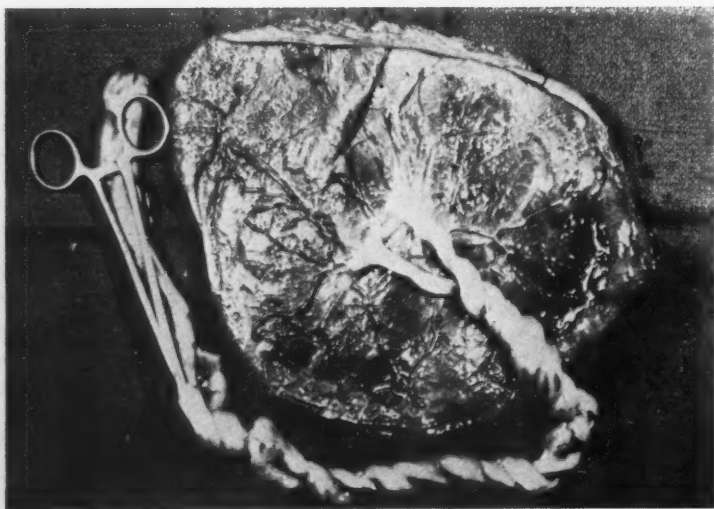


Fig. 3.

CASE 2.—Mrs. E. G., a 24-year-old gravida i, para 0, was admitted to the hospital on March 15, 1955, eight weeks prematurely, with a history of irregular uterine contractions. The patient had felt no fetal movement for the three weeks prior to admission. Examination showed a normal temperature and pulse. The blood pressure was 122/80. The abdomen

was gravid, the size of a 6 months' gestation, and was soft and nontender. No fetal heart tones were heard. The fetal membranes ruptured spontaneously during a pelvic examination two hours after admission, and the amniotic fluid was thick and dark brown. The first fetus was delivered almost immediately after rupture of the membranes from the left occiput posterior position. This fetus was a stillborn baby girl weighing 1 pound, 4 ounces. The second fetus was delivered as a breech, left sacrum anterior, six minutes later. This fetus was a stillborn baby girl weighing 1 pound, 14 ounces. The placenta was delivered spontaneously and immediately with the birth of the second twin. The placenta showed intertwining of the cords and contained five true knots. Both cords arose from the placenta 3 cm. apart and no partition was seen between them (Fig. 3). Both fetuses were macerated, indicating that they had been dead in utero for considerable time. The mother was discharged on March 18, 1955, in good condition after an uneventful postpartum course.

### Conclusions

1. Two cases of monoamniotic twin pregnancy are presented.
2. Both monoamniotic twins survived in one case.
3. Only 11 cases have been reported in the American literature (including the case reported here) of a double survival of monoamniotic twins.
4. After delivery of the first twin, prolapse of twisted or knotted umbilical cords or the absence of a second sac should suggest monoamniotic twins. Immediate delivery of the second twin should be accomplished.
5. Thorough examination of the placenta and umbilical cords of twin pregnancies should reveal a higher incidence of monoamniotic twins.

### References

1. Potter, E. L., and Crunden, A. B.: *AM. J. OBST. & GYNEC.* 42: 870, 1941.
2. King, J. A., et al.: *AM. J. OBST. & GYNEC.* 63: 691, 1952.
3. Quigley, J. K.: *AM. J. OBST. & GYNEC.* 29: 354, 1935.
4. Parks, J. L., and Epstein, J. R.: *AM. J. OBST. & GYNEC.* 39: 140, 1940.
5. McCormick, C. O.: *J. Indiana M. A.* 22: 245, 1929.
6. Conybeare, R. C.: *Obst. & Gynec.* 4: 444, 1954.
7. Hanes, M. V.: *Obst. & Gynec.* 4: 448, 1954.
8. Hagood, M., and Stokes, R. H.: *AM. J. OBST. & GYNEC.* 65: 1152, 1951.

## VAGINAL SEPTUM, A CAUSE OF DYSTOCIA\*

### Report of a Case

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CONGENITAL malformations of the female reproductive tract have always been a topic of considerable interest among obstetricians and gynecologists. Besides being anatomical curiosities, they may present unusual and difficult problems when associated with pregnancy. They probably occur more commonly than is generally believed, since they are often not recognized even when they cause actual disturbances of pregnancy. This observation is in keeping with other reports that many such cases are discovered only at the autopsy table, accidentally during an operation, or in the event of abnormal developments during pregnancy or labor.

The following case report illustrates dystocia caused by a complete longitudinal vaginal septum.

A 16-year-old white girl, para 0, gravida i, at term on Nov. 18, 1954, was first seen on June 8, 1954. Examination at that time was essentially normal and no abnormalities were noted. Her prenatal course was uneventful until Nov. 17, 1954, when abdominal examination showed the fetus to be in a breech position. X-ray pelvimetry demonstrated an adequate pelvis and a small fetus in frank breech position.

On November 19 at 7:00 A.M. the patient was admitted in active labor. The labor progressed satisfactorily. At 10:30 A.M. the membranes ruptured spontaneously and the breech was bulging at the introitus. The patient was taken to the delivery room and under general anesthesia and over a left mediolateral episiotomy was delivered by partial breech extraction of a full-term living female infant. The breech, trunk, shoulders, and arms were delivered slowly without difficulty. However, there was obstruction to the descent and rotation of the head. Examination showed the head to be in transverse position with a longitudinal vaginal septum passing under the chin holding the head in this position. The operator placed his hand between the septum and chin; then the head was rotated to an occiput anterior position and the Piper forceps were applied to the head, delivering it without difficulty.

Following delivery of the infant, the vagina was examined and the septum was found to extend from the vulva to the cervix. The cervix could be seen on either side of the septum. There were no other abnormalities noted. The septum was excised. The patient's postpartum course was uneventful. She was discharged on the sixth postpartum day.

At follow-up examination the intravenous pyelograms showed a normal kidney collecting system. A hysterosalpingogram disclosed a normal uterine outline and patent Fallopian tubes.

### Comment

At our clinic the patient is seen and examined by several qualified obstetricians during the prenatal course. The author's first contact with the

\*The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval service at large.

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patient was at the time of her admission to the hospital in active labor. In spite of the previous examinations by several physicians, the complete longitudinal vaginal septum was not discovered until delivery. This illustrates very clearly that the diagnosis of this anomaly is often missed during routine vaginal examination, especially if the septum is flattened out at the side of an apparently normal vaginal opening.

The diagnosis of congenital abnormalities of the uterus and vagina usually presents little difficulty if the obstetrician keeps them in mind. Once he has recognized the abnormalities, he will be aware of the complications to be anticipated during pregnancy and labor.

#### **Summary**

1. A case is reported of septate vagina producing complications during delivery of a frank breech.
2. This vaginal anomaly can produce complications during pregnancy and labor.
3. The importance of looking for anomalies of the genital tract during pelvic examination of the patient is stressed.

## CASE REPORT OF COEXISTENT BILATERAL TUBAL PREGNANCY

JULIAN WALDO ROSS, M.D., AND LIONEL A. DESBORDES, M.D., WASHINGTON, D. C.  
(From the Department of Obstetrics and Gynecology, Howard University and Freedmen's Hospital)

IN THE entire history of the obstetrical service at Freedmen's Hospital, never has a case of coexistent bilateral tubal pregnancy been encountered. Unilateral tubal pregnancies have been frequent and, indeed, on the increase since the advent of chemotherapy and antibiotics. Repeat ectopic pregnancies have been diagnosed in a small percentage of cases.

Since only 94 cases of coexistent bilateral tubal pregnancy have been reported in the literature up to 1953, it is not surprising that such a case has not been encountered here, before. Of bilateral simultaneous tubal pregnancies, Norris,<sup>1</sup> in 1953, reported the number of collected cases as follows: "Eden and Lochyer, in their textbook on Gynecology, reported 28 cases up to 1927. Fishback, in 1937, had collected 76 cases from the literature. Hall, in 1949, found 87 cases reported; and Abrams and Kanter, in 1948, found 94 cases reported to that date."

Fishback,<sup>2</sup> in 1939, set down as criteria for bilateral simultaneous tubal pregnancy that there should be a description of the fetuses or any portion of them found, as well as placental material. However, Norris stated that as the fetal parts and placental tissue are usually small and with some degree of degeneration, the demonstration of chorionic villi, microscopically, in each tube should be sufficient to establish the authenticity of coincidental bilateral tubal pregnancy.

The term nonsimultaneous has been used in describing these cases, to designate those which occurred at different times with a definite interval; and the term coexistent when pregnancies are present in both tubes but not necessarily of the same period of gestation.

### Case Report

Mrs. E. M. P. (No. 134584), a 26-year-old para i, gravida ii, a well-developed and well-nourished woman, was admitted to Freedmen's Hospital Sept. 27, 1955, with the chief complaints of bleeding and pain.

Her last normal menstrual period was June 18, 1955; the menstrual periods preceding this one were normal. She had been essentially well until about a month prior to admission when she began to have lower abdominal pain which was suprapubic and in the midline. This pain later was felt in the left lower quadrant, and about one month still later was felt, also, in the right lower quadrant, at times alternating, and at other times simultaneously in both lower quadrants of the abdomen.

Associated with the pain was vaginal bleeding, daily, requiring about one vaginal pad per day. She had, occasionally, dizzy spells but no frank syncope. There was no nausea, vomiting, or history of previous pelvic inflammatory disease.

Fig. 1.

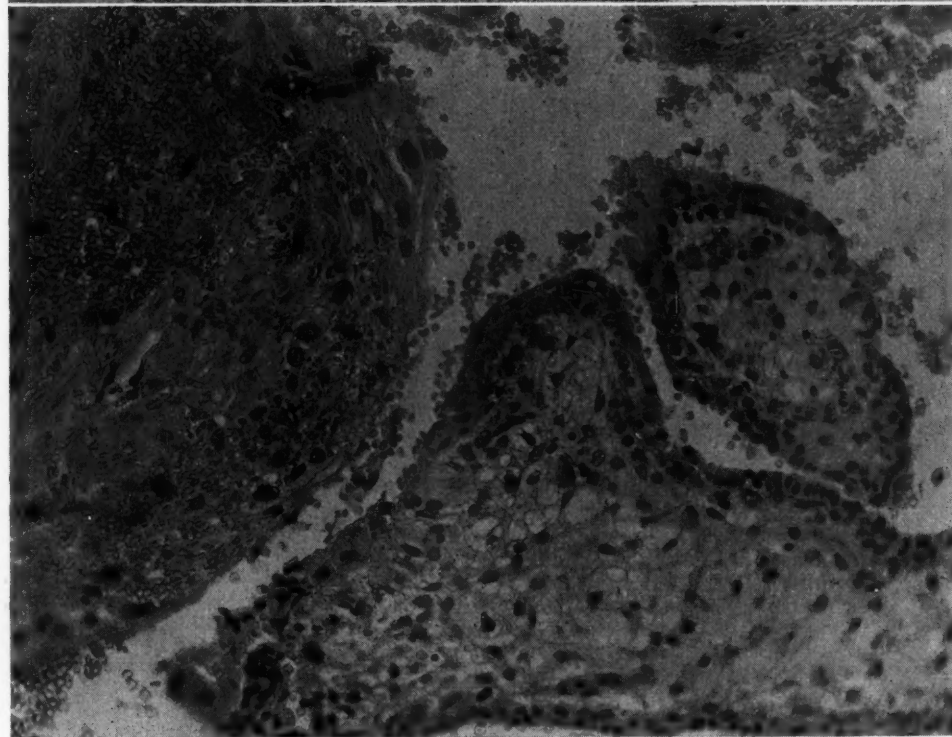
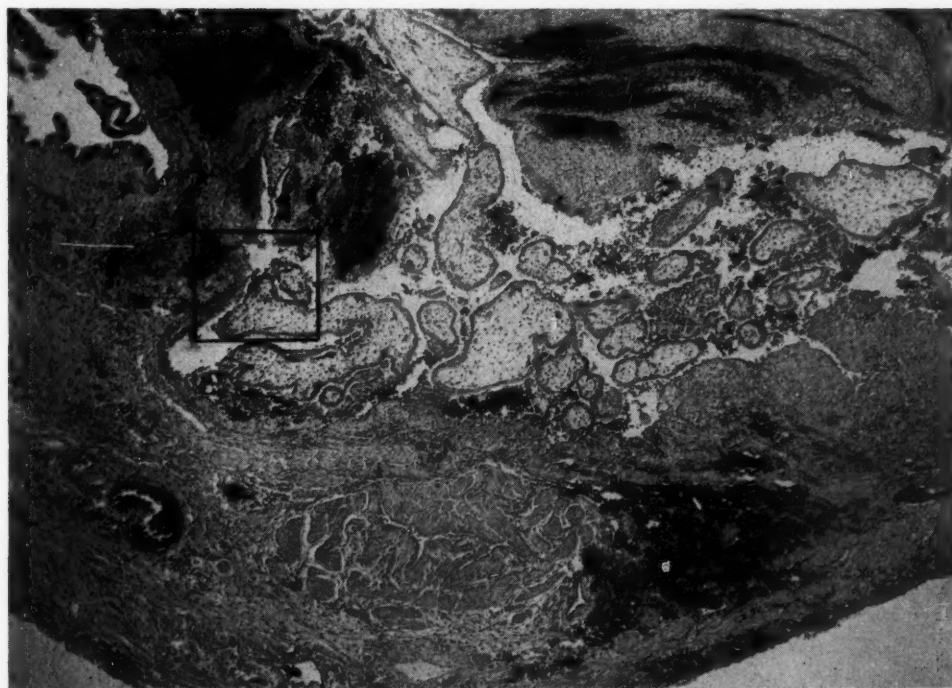


Fig. 2.

Fig. 1.—Low-power photomicrograph of left Fallopian tube, cross section, showing hemorrhage in tubal lumen and implantation site. ( $\times 15$ ; reduced  $\frac{1}{4}$ .)

Fig. 2.—Higher magnification of indicated area in Fig. 1, showing well-preserved chorionic villus and decidual reaction in lining of tube. ( $\times 160$ ; reduced  $\frac{1}{4}$ .)

Fig. 3.

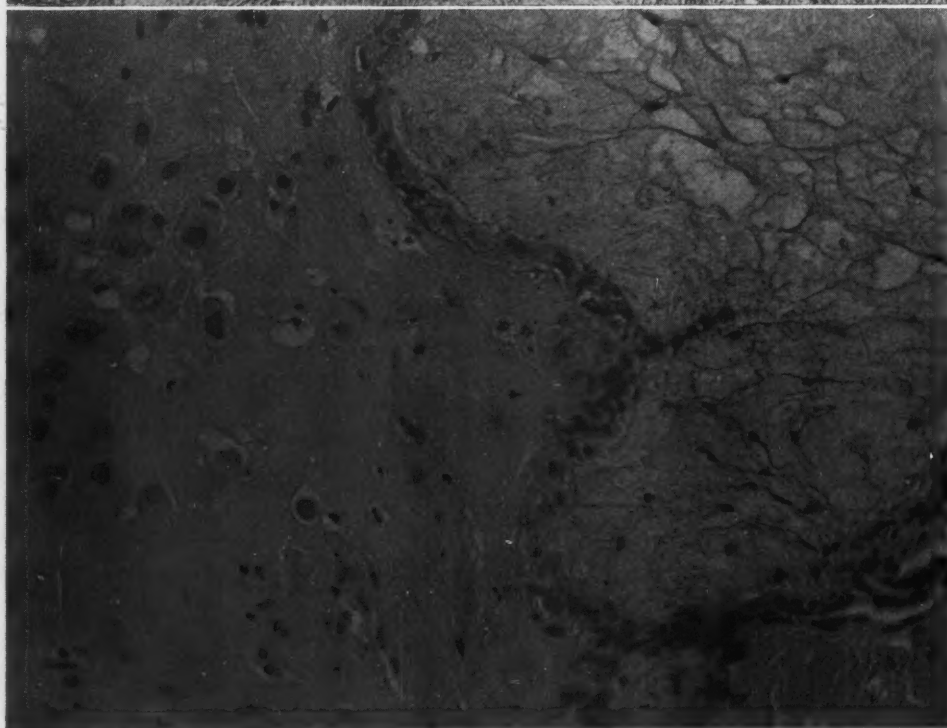


Fig. 4.

Fig. 3.—Low-power photomicrograph of right Fallopian tube, cross section, showing implantation site and hemorrhage in lumen. ( $\times 15$ ; reduced  $\frac{1}{4}$ .)

Fig. 4.—Higher-power photomicrograph of indicated area in Fig. 3, showing chorionic villus and decidua. ( $\times 300$ ; reduced  $\frac{1}{4}$ .)



*Physical Examination.*—This patient was an asthenic woman, cooperative, well oriented and in no acute distress. The blood pressure was 120/70, pulse 100, respirations 20, and temperature 99° F.

She had mild generalized abdominal tenderness and tenderness to palpation in the lower left quadrant. There was a suggestion of dullness in the flanks.

A vaginal and speculum examination showed the introitus to be parous, the cervix soft, dusky in hue, with several Nabothian cysts. There was isthmie compressibility. The uterus was soft and slightly enlarged. A soft, cystic mass about 4 cm. in diameter was felt in the left adnexal region. The cul-de-sac of Douglas had a boggy consistency. Pain was elicited on anterior traction of the cervix. Digital rectal examination disclosed no additional information.

A culdocentesis was productive of noncoagulable blood. The case was diagnosed as left ruptured tubal pregnancy with some pathological condition in the right adnexal region.

*Laboratory Findings.*—The white blood cell count was 15,750, red blood cell count 3.13 million, hemoglobin 7.62 Gm., Hematocrit 16, and erythrocyte sedimentation rate 30 (Wintrobe uncorrected). The nonprotein nitrogen was 22, serum glucose 93, and chloride 103. Urinalysis was negative except for a few bacteria and yeast cells.

After adequate preparation, the patient was immediately taken to the operating room for a laparotomy. This disclosed that the left tube was the seat of a hematosalpinx with evidence of products of conception, all of which was removed in a left salpingectomy. The right tube was inspected as part of the routine, and in the isthmie portion a somewhat firm, purple area about 2 cm. in length was observed. This section was removed and an end-to-end anastomosis of the tube was performed.

#### *Pathology.*—

*Gross:* One part of the specimen consisted of a portion of Fallopian tube including the fimbriated end which measured 6 cm. in length and varied in diameter from 0.7 to 3.0 cm. at the fimbriated end. Section across the lumen of the tube showed a bloody fluid within the lumen extending a distance of 5 cm. The wall of the tube appeared somewhat thickened. Proximal to the area of blood within the tube, the tubal lumen appeared normal and the walls did not appear to be thickened. A small perforation of the serosa of the tube was seen overlying the mass of blood in the tube. Another part of the specimen consisted of what appeared to be an expanded portion of tube and measured 2.5 cm. in length by 1.5 cm. in diameter. On section, it appeared to contain blood within the lumen.

*Microscopic:* Chorionic villi and venous sinuses were present in both parts and had eroded the wall at one point. The tubes showed thickening of the wall and blunting of the villi.

*Impression:* Ectopic gestation right and left Fallopian tubes. Perforation of the left tube.

The patient's postoperative course was uneventful. A tubal insufflation (Rubin) was performed Jan. 19, 1956, and a sustained rise in the pressure to 200 mm. of mercury was registered on three trials.

From the history, pelvic examination, clinical findings, and laboratory aids, the preoperative diagnosis of ruptured left tubal pregnancy was justifiable; because of the bilateral pelvic pain and the pelvic findings at laparotomy the co-existence of bilateral tubal pregnancy was highly suspected; but the demonstration of chorionic villi in each tube removed all question and the condition was designated an authentic case of coincidental bilateral tubal pregnancy.

#### **Conclusions**

1. A review of the literature revealing 94 cases of bilateral tubal pregnancy up to 1953 is presented.

2. Criteria for bilateral simultaneous tubal pregnancy have been cited.
3. Another case of coexistent bilateral tubal pregnancy is herein reported.

We acknowledge with appreciation the pathology and photomicrographs done in this case by the Department of Pathology of Howard University College of Medicine.

#### References

1. Norris, S.: Canad. M. A. J. 68: 379, 1953.
2. Fishback, H. R.: AM. J. OBST. & GYNEC. 37: 1035, 1939.

## EARLY PRIMARY ABDOMINAL (PERITONEAL) PREGNANCY

### Case Report

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*(From the Department of Obstetrics and Gynecology, Sacred Heart General Hospital)*

THERE has been a controversy concerning the ability of the fertilized human ovum to achieve primary nidation on any peritoneal surface. In cases of advanced abdominal pregnancy the placental attachments are extensive and it is not possible to determine the original site of nidation.

Studdiford<sup>1</sup> in 1942, in a report of a case of an early ruptured pregnancy on the posterior aspect of the uterus, proposed the following criteria upon which proof of a primary abdominal pregnancy must rest: (1) normal tubes and ovaries bilaterally with no evidence of recent or remote injury, (2) the absence of any evidence of a uteroperitoneal fistula, and (3) the presence of a pregnancy related exclusively to the peritoneal surface and young enough to eliminate the possibility of secondary implantation following a primary nidation in the tube.

The following is a case that meets these criteria.

A 22-year-old woman who had been divorced for 1 year was admitted to the emergency room March 11, 1955. Her chief complaint was severe pain in the abdomen. Her last menstrual period was Feb. 8, 1955, with her next period due March 8. She was three days overdue and had no sign of a period. There was no spotting and no vaginal bleeding. For the previous four days she had had pain in the rectum, particularly with bowel movements. Four hours before admission, during a bowel movement, she had a severe pain in the abdomen.

On admission she had a blood pressure of 92/50, pulse 100, boardlike rigidity in the abdomen, and shoulder pain. A diagnosis of ruptured ectopic pregnancy with intra-abdominal hemorrhage was made and the patient was taken to the operating room.

At operation approximately 2,000 c.c. of blood was found in the abdominal cavity. Both tubes were exposed and were found to be normal. The blood clots were scooped out of the abdomen to aid in finding the bleeding site.

In the pouch of Douglas at the rectal-vaginal junction there was a bleeding area about 3 cm. in diameter. While this area was being explored to find the cause of bleeding the circulating nurse found among the clots a small fetus enveloped in an intact amnion with an intact placenta. The size of the placenta corresponded exactly to the size of the bleeding area in the cul-de-sac. The bleeding was controlled with No. 0 chromic atraumatic sutures. Exploration of both tubes and ovaries showed no evidence of recent or remote injury and there was no evidence of a uteroperitoneal fistula. Following exploration the abdomen was closed. During and immediately after operation the patient received three blood transfusions. She was dismissed on the fourth postoperative day.

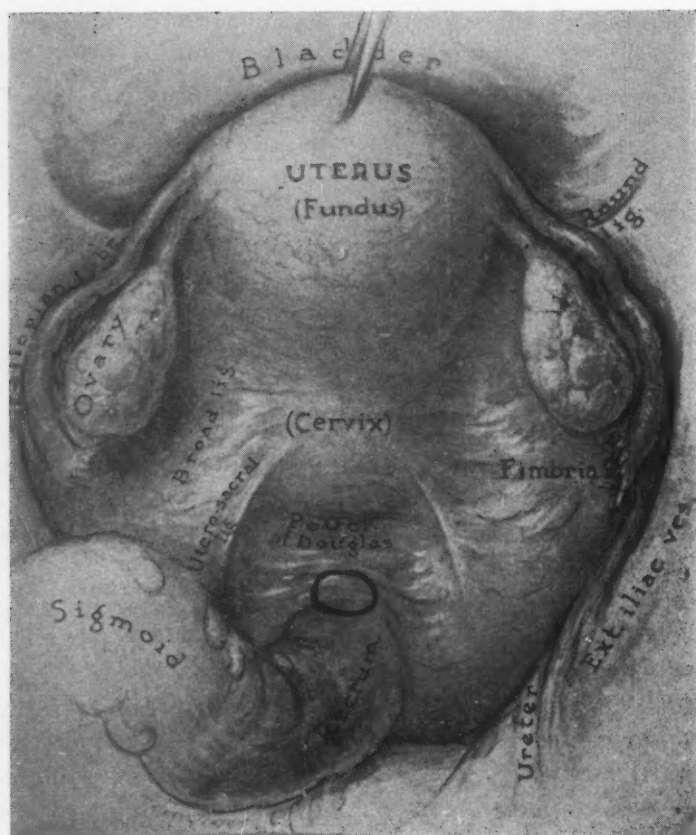


Fig. 1.—Diagram showing site of implantation.. (From Curtis, Arthur H.: *Textbook of Gynecology*, ed. 5, Philadelphia, 1946, W. B. Saunders Company.)

### Summary

A case of extrauterine pregnancy is presented that meets all of the criteria detailed by Studdiford necessary to be termed a primary abdominal pregnancy.

### Reference

1. Studdiford, William E.: *AM. J. OBST. & GYNEC.* 44: 487, 1942.



## INTRAMURAL PREGNANCY

### A Case Report

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**I**N THE many papers related to the different sites of extrauterine pregnancy, intramural pregnancy is rarely dealt with. This is the report of one such case seen on the Gynecology Service at The Baltimore City Hospitals.

Case No. 179065, Mrs. J. H. T., aged 25 years, was admitted to the Accident Room during the night of Jan. 24, 1954, complaining of abdominal pain, vomiting, and fainting. On Dec. 21, 1953, in our outpatient department she had been found to have a slightly enlarged and irregular uterus and was thought to have a normal intrauterine pregnancy. On Oct. 31, 1952, she had had a right salpingectomy and appendectomy for a ruptured tubal pregnancy. On the present admission, though in distress, she could react to questioning. Four hours before, while watching television, she felt a sudden, sharp lower abdominal pain, was helped to bed, and lost consciousness several times between vomiting spells. Her last normal menstrual period had been on Nov. 13, 1953. On examination the patient was very pale, dyspneic, with a blood pressure of 68/42, pulse 140 and very weak. The heart sounds were distant. The abdomen was somewhat distended, rigid, and tender to pressure and rebound. Pelvic examination showed the cervix to be in the axis of the vagina, closed, small, and painful on motion. The fornices were tense and very tender, so much so that the uterus and adnexa could not be palpated. The hemoglobin was 8.5 Gm. and the urine negative for albumin and sugar. She was placed in shock position, intravenous fluids started, and she was taken to the operating room with a preoperative diagnosis of left ruptured tubal pregnancy.

Under intratracheal gas-oxygen-ether anesthesia, the abdomen was entered through a right paramedian incision and 2,850 c.c. of free and clotted blood was found. In this were a two months' fetus and cord attached to a small placenta. Pelvic exploration disclosed a normal left tube and ovary containing a corpus luteum. The right tube had been previously removed. The right ovary was small and attached to the right cornu. Three centimeters from this, on the posterior fundal wall, there was a ragged, actively bleeding defect into the myometrium. A supracervical hysterectomy and right oophorectomy were done. The left tube and ovary were not removed.

During and following this procedure she was given 2,500 c.c. of whole blood and on the following morning had a normal blood pressure and hemoglobin (11 Gm.). Except for a slight febrile reaction on the second and third postoperative days, her recovery was uneventful until her discharge on the eighth day. Before discharge a cervical biopsy and smear were taken and proved negative.

**Pathology Report.**—The specimen consisted of a right ovary with a uterus showing a round defect (as described above) extending through the thickness of the myometrium, but no communication into the endometrial surface could be demonstrated. Diagnosis: (1) Ruptured ectopic pregnancy with implantation site in myometrium from serosa. (2) Fetus 9 cm. in length with umbilical cord and placenta attached. (Dr. Abou Pollack.)

In reviewing the literature, we find 3 cases similar to this, the last one being that of Buttenberg<sup>4</sup> in 1955. He credits Perli<sup>6</sup> with the first description of an intramural pregnancy in 1924, and Baniecki's<sup>3</sup> case as the second one in 1950. Buttenberg's case is identical with ours except for the previous

ectopic pregnancy. In the cases of Perli and Baniecki, laparotomy was performed prior to rupture and the pregnancies enucleated, with the uterus left in place. Two other cases differing from these 3 and from ours have been reported, one by Baniecki and the other by Achmatowicz,<sup>1</sup> both occurring in myomatous uteri. In the older literature, Von Rosenthal<sup>7</sup> described an interstitial pregnancy and Alexandroff,<sup>2</sup> Freund,<sup>5</sup> and Schickele<sup>8</sup> published cases in which there was a connection with the uterine cavity.

In considering the various hypotheses of pathogenesis, Perli suggested that the ovum becomes implanted in a deep endometrial gland. Buttenberg cited the hypothetical interpretation of Veit of penetration of a vein by the ovum and migration by this route to the myometrium. Baniecki, Achmatowicz, and Buttenberg suggest that nidation starts from the serosa. Of these hypotheses, the latter seems to fit our case, assuming that an intramural pregnancy must be separated from the uterine cavity and tube and be surrounded by uterine musculature.

#### References

1. Achmatowicz, L.: *Lancet* 2: 63, 1952.
2. Alexandroff, G.: *Monatschr. Geburtsh. u. Gynäk.* 12: 447, 1900.
3. Baniecki, H.: *Zentralbl. Gynäk.* 72: 162, 1950.
4. Buttenberg, D.: *Zentralbl. Gynäk.* 77: 1018, 1955.
5. Freund, W. A.: *Beitr. z. Geburtsh. u. Gynäk.* 4: 1, 1901.
6. Perli, H.: *Zentralbl. Gynäk.* 48: 2841, 1924.
7. Von Rosenthal, J.: *Zentralbl. Gynäk.* 20: 1297, 1896.
8. Schickele, G.: *Beitr. Geburtsh. u. Gynäk.* 8: 267, 1904.

## A CASE OF OSTEOPENIA IMPERFECTA CONGENITA DIAGNOSED IN UTERO\*

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**O**STEOPENIA imperfecta is a rare disorder characterized by marked fragility of the bones resulting in multiple fractures. Clear descriptions of this disease can be traced as far back as the year 1700 according to Watson-Jones.<sup>1</sup> In 1833 Lobstein<sup>2</sup> described this condition in which the fragility of the bones cannot be explained and designated it idiopathic osteopetrosis. Vrolik in 1846 (quoted by Snapper<sup>3</sup>) reported a case of fragilitas ossium at birth and named it osteopenia imperfecta. Looser<sup>4</sup> in 1906 was probably the first to distinguish between the congenital and late forms of osteopenia imperfecta. The syndrome of fragility of the bones associated with blue sclerae and deafness was later described by Voorhoeve<sup>5, 6</sup> in 1917 and 1919 and also by Key<sup>7</sup> in 1926. Up to the present time a great number of cases have been reported by different authors,<sup>8-22</sup> although the affection remains a rare one.

The syndrome is hereditary, and the congenital form is usually transmitted as a recessive Mendelian trait, while the late form is dominant. According to Potter,<sup>23</sup> it may appear as a result of mutation. Seerdorff<sup>24</sup> reported a study of the disease in 180 members of 55 Danish families, and in another report<sup>25</sup> it occurred in one instance in five generations. It is known that this disorder is a congenital osteoporosis but, unlike other conditions characterized by abnormal fragility of the bones, its etiology has not been discovered.

In osteopenia imperfecta there is a marked, generalized osteoporosis of the bones, of both cartilaginous and membranous origin, due to failure of periosteal apposition of bone and defective endosteal bone production. According to most authors, the osteoblasts are normal in appearance but reduced in number and activity, and deposition of bone around the matrix is minimal. At the same time osteoclasts remain active. The calvarium is extremely thin and in severe cases may consist of a membranous bag with isolated islands of bone tissue.<sup>23, 26</sup>

The bones are brittle and exhibit a very thin cortex. The trabeculae are reduced in number and in size and contain less calcium than normal.<sup>3, 23</sup> While the diaphysis of the long bones is deficient and slender, the growth and differentiation of the epiphysis remain normal, which accounts for the contrasting and swollen appearance of these bones.<sup>3</sup> The diameter of the bones may be normal or increased.<sup>27, 28</sup> Fractures, which are common occurrences, heal quickly, and callus formation and absorption are normally rapid and at times even excessive.<sup>1</sup>

\*Presented at a meeting of The Bronx Gynecological and Obstetrical Society, April 23, 1956.

The microscopic aspect of osteogenesis imperfecta has been described in detail by Snapper<sup>3</sup> who compares it to the picture seen in the fiber bone found in the embryonic stage. According to this author, the outstanding features are irregularity or even absence of bone lamellae in conjunction with the presence of wide canals and deficient matrix.

The severity of this condition is variable in degree and time of onset. The disease takes two forms, formerly considered as separate entities but now proved to be variants of the same condition:

1. The *congenital form*, osteogenesis imperfecta congenita, fragilitas ossium, osteopsathyrosis congenita,<sup>4</sup> or Vrolik's disease, is usually more severe than the late form with multiple fractures in the newborn or even in utero.

2. The *late form*, osteogenesis imperfecta tarda, Lobstein's disease, osteopsathyrosis tarda,<sup>4</sup> idiopathic osteopsathyrosis, Spurway's<sup>17</sup> disease, periosteal dysplasia, or van der Hoeve's syndrome,<sup>29</sup> is encountered in infants, adolescents, or adults.

Atypical cases and combinations of the two forms occur.

Signs and symptoms vary widely from very mild to severe. In general, the clinical picture is one of multiple and extensive angulations and deformities of the extremities resulting in disability and crippling or even dwarfism.<sup>30</sup> Blue scleras, middle ear deafness, and exaggerated mobility of the joints are frequently associated anomalies.

Laboratory findings in osteogenesis imperfecta are within normal limits. Serum calcium, phosphorus, and alkaline phosphatase are normal, although the latter may be slightly increased.

X-rays reveal multiple fractures at birth, including old fractures with callus formation and fresh ones due to trauma during and after delivery. Roentgenographic features consist of generalized osteoporosis and diminished density of the bones, as well as hypoplasia and thinning of the cortex with deficient spongiosa. Caffey<sup>26</sup> stated that a pattern of mosaic rarefaction of the bones of the skull is pathognomonic of the disease.

R. G. (Bronx Hospital No. 290690) was a 27-year-old white woman, gravida iii, para ii, whose last menstrual period was Feb. 26, 1955, and expected date of confinement was Dec. 5, 1955. The prenatal course was uneventful, and all laboratory tests were within normal limits.

The medical and surgical history were noncontributory. The family history was negative, and on both the father's and mother's sides no positive history of bone diseases could be elicited. The previous obstetric history disclosed that in 1947 she had had a normal delivery by low forceps of a full-term male child weighing 8 pounds, 8 ounces, in good condition and without any signs of pathologic changes of the bones. In 1950 the patient had a normal spontaneous delivery of a male child weighing 7 pounds, 11 ounces, without any pathologic bone changes. Both these children lead a normal life and have never sustained any fractures of the bones.

On Dec. 6, 1955, the patient was admitted in mild labor. After several hours, rectal examination revealed a frank breech presenting in left sacroanterior position, and x-ray pelvimetry was ordered. The x-ray pelvimetry studies of the mother taken during labor showed many changes in the fetal skeleton (Fig. 1):

1. Deformity of ribs due to multiple healed fractures.



2. Fracture of a midfemoral shaft of the fetus with abundant callus and apparent pseudarthrosis formation in the right lower quadrant. Angulation deformity of the lower aspect of a humeral shaft secondary to previous fracture was demonstrated in the right upper quadrant. Old fracture of the ulnar shaft with abundant callus formation was also seen.

On Dec. 7, 1955, after 19 hours of first stage and 30 minutes of second stage labor, the patient delivered a 6 pound, 10 ounce, male infant. She was permitted to push the baby out with voluntary efforts to the umbilicus. The trunk and shoulders were then delivered by gentle traction on the fetal pelvis and the head by the Mauriceau-Smellie-Veit maneuver under gas-oxygen-ether anesthesia with a right mediolateral episiotomy. At no time during this whole procedure was any traction or pressure applied to the fetal lower extremities.



Fig. 1.—Pelvimetric study showing multiple old fractures of the fetal bones, healed with abundant callus formation.

Examination of the baby showed a 6 pound, 10 ounce baby boy in good general condition. Palpation disclosed crepitation along both lower legs and thighs. The baby's skull was of normal shape, but the bones were rather thin and parchmentlike; the anterior fontanel was abnormally large. X-ray films of the infant showed more clearly changes observed in the antepartum x-rays (Fig. 2).

1. Multiple healed fractures of all the ribs. (Potter<sup>23</sup> described these healing fractures of the ribs as "strings of beads.")

2. Healed fracture of the lower aspect of the right humerus. Fracture of the mid-shaft of the right radius with abundant callus. Recent fracture of the right ulnar shaft.

3. Recent and old multiple fractures of both femoral shafts and recent fractures of both tibias and fibulas.

The other bones of the body did not appear to be deformed.

X-ray films of the infant taken at the age of 8 weeks showed good healing of all fractures with marked callus formation. Deformities of the child's extremities are minimal.



Fig. 2.—View of the baby taken on the day of birth showing multiple old and recent fractures of the lower extremities.

#### Comment

This is a case of osteogenesis imperfecta congenita; the prenatal or fetal type, according to Fairbank.<sup>31, 32</sup> The anomaly is characterized by multiple bone fractures with excessive hyperplastic callus and the formation of false joints while the fetus is in utero. Consequently, the disease is well advanced before birth and may be identified on prenatal x-ray films as in the case presented. Other isolated cases of this rare type have been reported.

On the Obstetrical Service of the Bronx Hospital pelvimetry is routinely performed in all cases of breech or other abnormal presentations, in cases of bleeding, and in most primiparas at or near term or during labor. In this case of a multipara with a breech presentation, routine x-rays showed the presence of multiple healing or healed fractures of the fetal bones with marked callus formation.

In determining the most advisable method of delivery for an infant presenting this abnormality one must weigh the relative risks to both the mother and child by vaginal and abdominal routes. In our case gently assisted delivery from below was performed.

The case reported herein is the first instance of osteogenesis imperfecta congenita in this hospital in a twenty-year period and represents an incidence of 1:40,000 deliveries.

### Summary

A case of osteogenesis imperfecta congenita is reported in which the diagnosis of the condition was made before delivery with the aid of x-ray films.

We wish to express our thanks and appreciation to Dr. A. J. Bernstein, Director of Diagnostic Radiology, Bronx Hospital, and to Dr. J. Lapin, Attending Pediatrician, for their cooperation.

### References

1. Watson-Jones, Sir R.: *Fractures and Joint Injuries*, ed. 4, Baltimore, 1955, Williams & Wilkins Company, vol. 1.
2. Lobstein, J. F.: *Lehrbuch der pathologischen Anatomie*, Stuttgart, 1835, vol. 2, p. 179.
3. Snapper, I.: *Medical Clinics on Bone Diseases*, New York, 1949, Interscience Publishers, Inc.
4. Looser, E.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* 15: 161, 1906.
5. Voorhoeve, N.: *Nederl. tijdschr. v geneesk.* 61: 1399, 1917.
6. Voorhoeve, N.: *Lancet* 2: 740, 1917.
7. Key, J. A.: *Arch. Surg.* 13: 523, 1926.
8. Aitken, G. W., Cohen, A., and Verco, P. W.: *J. Fac. Radiol. (London)* 6: 1, 1954.
9. Bromer, R. S.: *Am. J. Roentgenol.* 30: 631, 1933.
10. Bronson, E.: *Edinburgh M. J.* 18: 240, 1917.
11. Cecil, R. L., and Loeb, R. F.: *A Textbook of Medicine*, ed. 9, Philadelphia, 1955, W. B. Saunders Company.
12. Eddowes, A.: *Brit. M. J.* 2: 222, 1900.
13. Holt, L. E., Jr., and McIntosh, R.: *Pediatrics*, ed. 12, New York, 1953, Appleton-Century-Crofts, Inc.
14. Howorth, B.: *A Textbook of Orthopedics*, Philadelphia, 1952, W. B. Saunders Company.
15. Kaplan, E. B.: *J. Bone & Joint Surg.* 16: 625, 1934.
16. Ottley, C. M.: *Arch. Dis. Childhood* 6-7: 137, 1931-1932.
17. Spurway, J.: *Brit. M. J.* 1: 826, 1917; 2: 845, 1936.
18. Swanson, W. W., and Iob, U.: *Am. J. Dis. Child.* 49: 95, 1935.
19. Weber, M.: *Arch. Path.* 9: 984, 1930.
20. Brailsford, J. F.: *The Radiology of Bones and Joints*, ed. 4, London, 1948, J. & A. Churchill, Ltd.
21. Danelius, G.: *Arch. Gynäk.* 154: 161, 1933.
22. Frerking, H. W., and Zink, O. C.: *Am. J. Roentgenol.* 67: 103, 1952.
23. Potter, E. L.: *Pathology of the Fetus and the Newborn*, Chicago, 1953, The Year Book Publishers, Inc.
24. Seerdorff, K. S.: Cited by Watson-Jones.<sup>1</sup>
25. Burch, G. E., and Sodeman, W. A.: *Am. J. M. Sc.* 194: 844, 1937.
26. Caffey, J.: *Pediatric X-Ray Diagnosis*, Chicago, 1950, The Year Book Publishers, Inc.
27. Fairbank, H. A. T.: *J. Bone & Joint Surg.* 30B: 164, 1948.
28. Fairbank, H. A. T.: *An Atlas of General Affections of the Skeleton*, Edinburgh, 1951, E. & S. Livingstone.
29. Van der Hoeve, J., and de Kleyn, A.: *Arch. Ophth.* 95: 81, 1918.
30. Watson, E. H., and Lowrey, G. H.: *Growth and Development of Children*, Chicago, 1951, The Year Book Publishers, Inc.
31. Fairbank, H. A. T.: *Proc. Roy. Soc. Med.* 28: 1611, 1935.
32. Fairbank, H. A. T., and Baker, S. L.: *Brit. J. Surg.* 36: 1, 1948.

## AN UNSUSPECTED SOURCE OF A-B-O SENSITIZATION

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**D**URING the immunization of rabbits with a commercial preparation of gonadotropin in an attempt to produce specific antibodies against the hormone, an interesting phenomenon was observed which stimulated an investigation of the ability of this preparation to inhibit anti-A and anti-B agglutinins. Weak but apparently specific inhibition was observed, similar in degree and kind to the weak group-specific inhibition obtained with human plasma. This observation suggested the possibility that injection of this preparation into human subjects might stimulate a rise in the titer of the A and B isoantibodies. The purpose of this paper is to report a study on the group-specific antigenicity of this hormone preparation.

### Materials and Methods

The subjects selected for the experiment were patients on the wards of Bellevue Hospital who had previously been surgically sterilized. Four group O patients completed the course of injections and returned for follow-up antibody titrations. A sample of blood was drawn from each subject before the injections were started and another sample was drawn ten days after the last injection of the series was given.

The commercial preparation\* used in these studies is a brand of chorionic gonadotropin, which is extracted from the pooled urine of pregnant women.

The injections were given intramuscularly in daily doses of 3,000 I.U. each. One subject was given two such injections; 2 subjects received four injections each; while one subject was given five daily injections.

The titrations were carried out in the usual way by the tube agglutination method against fresh 2 per cent cell suspensions of groups O, A<sub>1</sub>, A<sub>2</sub>, and B. One set of titrations was carried out in saline medium, and a second by the acacia conglutination method. The technique has already been described in detail elsewhere.<sup>1</sup> In Case 1, where the first striking result was obtained, the titrations were repeated on a different day with different test cells with virtually identical results. In this case, the average of the two titrations was taken as the final result.

### Results

The findings are summarized in Table I. As shown in the table, in 2 of the 4 cases (Patients 1 and 3) there was a striking rise in the titer of the A and B isoantibodies. The titer for group A test cells was approximately fifteen to

\*The commercial preparation used in this study is Ayerst "A.P.L." brand of chorionic gonadotropin.



thirty times as high after the injections as before. while there was a four- to eightfold increase in titer for group B cells. In the other two cases the change in antibody titer was within the limits of error of the titration method. One of these subjects (Case 2) was already strongly sensitized to the A and B factors before the injections were given, which could explain her refractoriness to further stimulation.

TABLE I. THE EFFECT OF INJECTIONS OF CHORIONIC GONADOTROPIN ON THE TITERS OF A AND B ISOANTIBODIES

PATIENT (ALL GROUP O)	NUMBER OF DAILY INJECTIONS* OF HOR- MONE	TIME OF TEST	TITERS IN SALINE MEDIA FOR				TITERS IN ACACIA FOR			
			O	A <sub>1</sub>	A <sub>2</sub>	B	O	A <sub>1</sub>	A <sub>2</sub>	B
1. M.K.	5	Preinjection (4/23/56)	0	30	15	35	0	120	60	100
		Postinjection (5/8/56)	0	460	230	100	0	2,500	2,000	400
2. F.P.	4	Preinjection (4/23/56)	0	120	60	40	0	2,500	2,000	800
		Postinjection (5/7/56)	0	70	20	20	0	1,800	900	320
3. A.C.	4	Preinjection (4/23/56)	0	30	8	8	0	70	30	20
		Postinjection (5/7/56)	0	480	240	80	0	1,900	1,700	160
4. M.M.	2	Preinjection (3/12/56)	0	15	8	20	0	400	80	60
		Postinjection (3/25/56)	0	60	40	30	0	800	240	60

\*Each dose consisted of 3,000 units of A.P.L.

The recommended dose for treating habitual abortion is 1,000 to 2,000 units repeated one or more times daily until the danger of abortion has passed.

These findings therefore demonstrate unequivocally that injections into human subjects of the preparation of chorionic gonadotropin used can stimulate a marked rise in titer of the A and B isoantibodies.

### Comment

A-like and B-like substances are ubiquitous in nature, and it is well known that injections into human subjects of many substances with A- and B-like properties can stimulate a marked rise in the titer of the A and B isoantibodies. In fact the natural A and B isoantibodies are believed to be of heterogenetic immune origin due to infection with microorganisms and ingestion of foods containing A- and B-like substances.<sup>2</sup> Marked rises in A and B isoantibody titers have been observed in human subjects receiving injections of tetanus antitoxin prepared in horses, transfusions of pooled human plasma, transfusions of group O blood conditioned with Witebsky A and B blood-group substances and intramuscular injections of autoclaved saliva.<sup>3</sup> Since human urine is known to contain A and B blood-group substances, the observation that injections of hormone preparation extracted from the human urine can cause a rise in isoantibody titer is not unexpected. Since A and B sensitization is believed to be one of the many causes of repeated abortions, as well as hemolytic disease of the newborn, it would be ironical indeed if it should turn out that injections of this hormone preparation can cause the very condition it is intended to prevent or correct.

### Summary

Injections into human subjects of chorionic gonadotropin prepared from pooled human pregnancy urine can stimulate a marked rise in A and B isoantibody titer. This suggests that the use of such material as a therapeutic agent during pregnancy is inadvisable.

### References

1. Wiener, A. S., Wexler, I. B., and Hurst, J. G.: *Blood* 4: 1014, 1949.
2. Wiener, A. S.: *J. Immunol.* 66: 51, 1951.
3. Wiener, A. S., Samwick, A. A., Morrison, H., and Cohen, L.: *Exper. Med. and Surg.* 13: 267, 1955.

## Reviews and Abstracts

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### Review of New Books

**Cytologic Technics for Office and Clinic.** By H. E. Nieburgs. 233 pages with 171 figures. New York, 1956, Grune & Stratton. \$7.75.

Although there are many different textbooks dealing with each aspect of cytology, there has been no one book that covered all aspects. Consequently, this book fills a real need. All methods of obtaining material for cytologic examination are described in a concise, clear manner. Microscopic descriptions are not extensive, but are adequate. All staining techniques in use today are described.

**Integrated Gynecology: Principles and Practice.** By I. C. Rubin and Joseph Novak. Three volumes, 1,925 pages with 509 figures. New York, 1956, The Blakiston Division, McGraw-Hill Book Company. \$60.00.

Three volumes with a total of almost 2,000 pages mark the culmination of many years of work on the part of I. C. Rubin of New York and Joseph Novak, formerly of Vienna. These are men of stature and far-reaching reputation. To their *Integrated Gynecology* they each bring a full lifetime of experience.

With real appreciation for the tremendous effort necessary to compile a work of this magnitude, it was with increasing disappointment and frustration that this reviewer perused the volumes. By far the best section is that concerning genital malignancy. Here the text is concise, up to date, and informative. The photomicrographs are particularly well selected and reproduced with unusual clarity and brilliance.

The section on the relationship of the reproductive system to other body systems furnishes interesting reading, particularly from the historical point of view. Granted many of the references are old and fall into the realm of speculation rather than scientific fact, nevertheless, there is much here from the life experience of the practitioner that is provocative.

These volumes are said to be for the medical student and the general practitioner. One might seriously consider whether any work in gynecology could possibly satisfy the needs of both. Texts for medical students should be stimulating to thought, and yet concise, modern, and accurate. The general practitioner expects the specialist author to select from his broad knowledge only that material which is modern, accurate, and entirely practical. Unfortunately *Integrated Gynecology* falls short in many respects. The writing is frequently superficial and discursive and the subject matter, while broad, often is lacking in discrimination and is dated. There are some inaccuracies, as for example, the chart on the excretion of chorionic gonadotropin in pregnancy (volume 1, page 228) shows a prolonged high level.

Perhaps these volumes point a way for a new kind of text in gynecology. However, if space were present to be filled by a scholarly text on integrated gynecology, satisfactory for student and general practitioner alike, it still remains vacant.

The price of \$60 is exorbitant.

**Observations on Krebiozen in the Management of Cancer.\*** By A. C. Ivy, John F. Pick, and W. F. Phillips. 88 pages with tables and plates. Chicago, 1956, Henry Regnery Company. \$2.50.

*Observations on Krebiozen in the Management of Cancer* purports to advance evidence in support of the senior author's claims made some years ago concerning a material alleged to be useful in treating cancer. The conclusions, which are based on reports of treated patients, are that the substance used, which has never been clearly defined, has brought about some improvement in a substantial proportion of the patients treated. The authors state that the improvement effected has occurred independently of other forms of treatment and too frequently to be considered examples of the well-known tendency of cancer to improve temporarily without any treatment. These claims are made for 4 per cent of 189 patients.

The alleged material to which the term *Krebiozen* is applied is described as being made from the blood serum of horses that have been treated with a particular strain of microorganism. The method of preparation is not given in sufficient detail to permit it to be repeated by others. This extent of detail is normally required of those who advance claims for the therapeutic usefulness of a new drug.

The book refers to experiments on spontaneous tumors in dogs and cats. The number and reproducibility of these experiments on such notably unreliable investigative material are not impressive.

There is much reference, of a general nature, to defense mechanisms against cancer, spontaneous regressions of the disease, and the role in cancer of the reticuloendothelial system. These references are of a conventional type, from statements of others hallowed by long usage but without documentation.

The clinical reports presented do not lend themselves to analysis or permit any conclusion about the validity of the authors' claims. Similar claims have been examined, repeatedly, by responsible agencies and found to be invalid. One would hope, therefore, that the ones published in this document would be carefully reviewed by impartial and informed individuals, and endorsed, before they are accepted.

C. P. RHOADS

**Practical Pediatric Dermatology.** By M. Leider. 433 pages with 115 illustrations. St. Louis, 1956, The C. V. Mosby Company. \$10.50.

This manual of pediatric dermatology is the product of a famous clinic and carries the clinic's banner in the form of an introduction by Dr. Marion B. Sulzberger. There are many good illustrations, all black and white, and the arrangement of the text is convenient. Much good advice of a practical nature is presented. In addition, the author makes an effort to explain diseases of the skin and their treatment in terms of mechanisms, in so far as this can be done; however, the empiricism of medicine has always been prominent in the treatment of the skin. The author supplies a formulary of 101 useful preparations, a figure which suggests that he wisely clings to magic numbers when necessary. Pediatricians and general practitioners should find this a useful book to have at hand.

**Tuberculose utero-annexielle.** By J. Bret and R. Legros. 146 pages with 60 illustrations. Paris, 1956, Masson et Cie. 1,600 fr.

Although the classic form of tuberculosis of the female organs is relatively rare, latent and deceptive forms, as revealed by research in the field of sterility, are common. Diagnostic methods are discussed with emphasis upon use of histologic examinations and hysterosalpingograms. There have been numerous publications dealing with genital tuberculosis, but there has been no agreement in regard to treatment. The authors discuss the

\*This review originally appeared in *Science* 125: 198, 1957, and is printed here with permission of Dr. Rhoads and Mr. DuShane, Editor of *Science*.



use of antibiotics and consider them fundamental. Cortisone in conjunction with antibiotics is most effective. Surgical treatment is usually conservative. The author deals with the problems of congenital tuberculosis in the newborn.

**The Merck Manual.** Edited by C. E. Lyght, W. P. Boger, G. A. Cardon, A. Gibson, and D. W. Richardson. Ninth edition, 1,870 pages. Rahway, 1956, Merck & Co. \$6.75.

The handy *Merck Manual* has been edited and brought up to date. It is printed on good quality paper and, although the print is small, it is very readable. The first 1,718 pages are devoted to specific diseases and disturbances and include their diagnosis and treatment. One of the most important features for the clinician is the group of prescriptions at the end of each section. The last pages of the book are devoted to descriptions of routine procedures.

It is unusual to find all of this material in one place and herein lies the importance of the book, which is useful for the practitioner, house officer, and medical student.

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## Books Received

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*The following books have been received. Selected reviews will appear in later issues.*

**Clinical Use of Radioisotopes.** By W. H. Beierwaltes, P. C. Johnson, and A. J. Solari. 456 pages with 117 illustrations. Philadelphia, 1957, W. B. Saunders Company.

**Congenital Anomalies of the Viscera: Their Embryological Basis.** By J. L. Bremer. 202 pages with 87 illustrations. Cambridge, 1957, Harvard University Press. \$5.00.

**The Gist of Obstetrics.** H. B. Atlee. 327 pages with 88 illustrations. Springfield, Ill., 1957, Charles C Thomas, Publisher. \$6.00.

**Modern Office Gynecology.** By G. Blinick and S. A. Kaufman. 218 pages with 47 figures. Philadelphia, 1957, Lea & Febiger. \$4.50.

**The Physician-Writer's Book . . . Tricks of the Trade of Medical Writing.** By R. M. Hewitt. 415 pages. Philadelphia, 1957, W. B. Saunders Company. \$9.00.

**Pregnancy and Birth.** By A. F. Guttmacher. 335 pages. New York, 1957, Viking Press. \$4.50.

## Selected Abstracts\*

### American Journal of Surgery

*Vol. 92, September, 1956.*

\*Howland, W., Boyan, C. P., and Schweizer, O.: Ventricular Fibrillation During Massive Blood Replacement, p. 356.

**Howland, Boyan, and Schweizer: Ventricular Fibrillation During Massive Blood Replacement, p. 356.**

The authors present two cases, one in which large blood replacement resulted in ventricular fibrillation and the other in tetany. A review of 253 cases in which 2,500 ml. or more of citrated blood was given discloses that ventricular fibrillation developed in 9 patients. The authors feel that a decreased amount of calcium ion, hypothermia, and rapid citrated blood transfusion all play etiological roles. To prevent ventricular fibrillation during surgery, replacement of blood as it is lost and administration of calcium salts are important. A continuous electrocardiogram and measurement of venous pressure are helpful.

R. KNAPP

### British Medical Journal

*Vol. 2, December 15, 1956.*

\*Russell, J. K., and Smith, D. F.: Foetal Exsanguination Associated With Surgical Induction of Labour, p. 1414.

**Russell and Smith: Foetal Exsanguination Associated With Surgical Induction of Labour, p. 1414.**

The authors report 2 perinatal deaths associated with elective induction of labor by rupture of the membranes. In both instances, fetal blood vessels in the membranes had been torn.

This is a rare complication of induction of labor, but one which must always be considered. The authors emphasize the need for a rapid, simple, reliable test for differentiating fetal from maternal blood. By such a test, one might elect to do a cesarean section in an effort to save the fetus.

J. EDWARD HALL

### Deutsche Medizinische Wochenschrift

*Vol. 81, No. 31, August 3, 1956.*

Knoerr, K., and Wallner, A.: On the Etiology of Puerperal Mastitis and of Infections in the Newborn, p. 1219.

*Vol. 81, No. 32, August 10, 1956.*

Frenzel, K. H., and Geissler, R.: Tissue Therapy in Leukorrhea Due to Ectropion, p. 1280.

*Vol. 81, No. 33, August 17, 1956.*

Philipp, E.: Malformations of the Gonads, p. 1298.

\*Titles preceded by an asterisk are abstracted below.

*Vol. 81, No. 34, August 24, 1956.*

Maier, E.: Precocious Puberty; Early, Normal, and Late Menarche, p. 1354.

*Vol. 81, No. 38, September 21, 1956.*

\*Philipp, E.: Anoxia in the Newborn, p. 1530.

\*Kirchhoff, H., and Kepp, R. K.: Results of Radiation Therapy With a Pendulum Source in Gynecologic Practice, p. 1535.

\*Wimhoefer, H., and Bach, H. G.: Improved Results and Changed Indications in Cesarean Section, p. 1541.

Martius, G.: Analgesia in Childbirth, p. 1547.

\*Hartl, H., and Langer, H.: Results of Plastic Operations on the Fallopian Tubes for Sterility, p. 1551.

Cramer, H.: Colposcopy for Diagnosis of Carcinoma of the Cervix, p. 1553.

Zeitz, H., and Stoll, P.: Damage to the Tube Following Hysterosalpingography With an Iodine-Oil Contrast Medium, p. 1557.

**Philipp: Anoxia in the Newborn, p. 1530.**

The etiology and therapy of hypoxia in the perinatal period are discussed. Oxygen lack of the fetus in utero near term can be due to: toxemia, sclerosis of placental vessels, placenta previa, prolapsed cord, tumultuous labor, narcotization, and medical disease (e.g., heart disease) in the mother. In all these cases, the baby benefits from early, easy delivery. Low forceps and episiotomy are indicated to shorten the second stage. In selected cases midforceps or cesarean section is the method of choice. The author considers postmaturity an important factor in sclerosis of placental vessels.

The frequently held view that the fetus normally suffers from oxygen lack is denied. The infant is adapted to relatively low oxygen tensions by his high hemoglobin concentration and the high dissociation curve of the hemoglobin.

The treatment is primarily prophylactic and includes avoidance of excessive use of opiates and barbiturates in labor, limitation of operations for delivery to those which are properly indicated, resolute action in operations, and administration of oxygen to the mother.

Anoxemia of the newborn can result from congenital anomalies of the brain or cardio-respiratory system, damage to the medullary respiratory center, and hyaline membrane disease. Congenital anomalies, even when they are amenable to treatment, are outside the realm of the obstetrician. Medullary damage and hyaline membrane disease are frequently found in premature infants. Therefore, the aim of the obstetrician is to reduce prematurity. Oxygen may be introduced into the stomach, but retrolental fibroplasia is always a danger when oxygen is used on a newborn infant. Analeptic drugs, except for lobeline, are generally not useful.

WALTER F. TAUBER

**Kirchhoff and Kepp: Results of Radiation Therapy With a Pendulum Source in Gynecologic Practice, p. 1535.**

Thirty-four patients with recurrences of cervical carcinoma were treated with a pendulum source of radiation. In some cases an intravaginal cone was also used. Seven patients were clinically cured after one year. This is 20.5 per cent, and is no better than results from older methods, but the danger of fistula formation is much reduced. Good palliative results were observed in many of the other women.

WALTER F. TAUBER

**Wimhoefer and Bach: Improved Results and Changed Indications in Cesarean Section, p. 1541.**

From 1935 to 1954 the cesarean section rate at the University of Heidelberg was 4.3 per cent (1,186 sections in 27,336 births). This is somewhat higher than the 3 per cent

\*Titles preceded by an asterisk are abstracted below.

ideal accepted widely in Germany. The authors, however, point to improved fetal and maternal results. From 1935 to 1939 the uncorrected maternal mortality rate was 8.8 per cent; from 1950 to 1954 the rate was 1.5 per cent. The corrected mortality from 1945 to 1954 was 0.8 per cent.

In the 20 years under discussion, the rate of cesarean section has remained essentially unchanged, but fewer operations are done for disproportion, placenta previa, and toxemia, and more are done for fetal indications. The last group has risen from 10.7 per cent to 35.2 per cent. During the last 10 years, the fetal mortality rate was 3.5 per cent.

WALTER F. TAUBER

**Hartl and Langer: Results of Plastic Operations on the Fallopian Tubes for Sterility, p. 1551.**

Results are reported of surgery for sterility at the University of Göttingen between 1926 and 1953. Follow-up was possible in 195 ward and 204 private patients. The overall result of at least one pregnancy following operation was obtained in 46.4 per cent of ward and 64.2 per cent of private patients. One hundred eighteen ventral fixations were done for malposition with 71.2 per cent success. Thirty-eight myomectomies resulted in pregnancy in 55.3 per cent of the women. All 5 patients who had reconstructive operations for bicornate uterus became pregnant and carried to term. The remainder of the patients had pelvic inflammatory disease, usually following postabortal infections or appendicitis. Patients with genital tuberculosis were not included in the series.

The simpler the operation, the greater the success. Among 25 patients who underwent extensive tubal plastic procedures, 14 with reimplantations of the tubes, and 3 with transplanted ovaries, no term pregnancies were reported. Tubal pregnancy followed reimplantation of tubes of one patient. Salpingolysis, the simple freeing of adhesions and opening of the fimbriated ends by a single incision with scissors, was done in 138 patients with 49.3 per cent subsequent pregnancies; however, 4 aborted, 7 had tubal pregnancies, and only 57 bore living children. Salpingostomy was done in 58 patients with 6 subsequent pregnancies (4 tubal). An increased proportion of success paralleled the greater frequency of salpingolysis in the last 13 years of the series.

The authors reject the use of plastic catheters, feeling that these can only bring about a foreign-body reaction. The results from salpingolysis of 49.3 per cent success (55.7 per cent in private patients) are markedly better than the 20 per cent reported by Bunster in 1951 and the survey published by Siegler and Hellman in 1956 (24 per cent of 931 cases). The authors consider that their favorable results stem from careful selection of patients and scrupulous operative technique, including careful handling of tissues and minimal surgery.

### Fertility and Sterility

*Volume 7, September-October, 1956.*

- \*Moore, J. G.: Tissue-Culture Studies of Endometrium Explanted at Varying Stages of the Menstrual Cycle, p. 411.
- \*Frank, L. G., and Gordon, T.: Reproductive Performance of Women With Pelvic Pain of Long Duration: Some Observations on Associated Psychopathology, p. 440.
- \*Tompkins, P.: Preservation of Fertility by Conservative Surgery for Ectopic Pregnancy: Principles and Report of a Case, p. 448.

**Moore, J. G.: Tissue-Culture Studies of Endometrium Explanted at Varying Stages of the Menstrual Cycle, p. 411.**

Tissue-culture methods offer the opportunity of studying dynamic tissue in both its structural and functional aspects. Endometrial tissue obtained at the time of curettage or endometrial biopsy was divided into two portions, one for histologic section and the other for tissue culture. A special nutritive medium was replaced every three to seven



days as indicated by variations in the pH. The preparations were maintained for 30 to 60 days. The explanted tissue was obtained from 22 patients with varying types of endometrium.

The endometrium explanted from any phase of the menstrual cycle seemed to grow with approximately the same vigor. The cell type of the principal growth component, while not unequivocally identified, seemed to be epithelial. Special stains for glycogen in new growth from explants of both proliferative and secretory endometrium were negative. The presence of epithelial cells in the new growth of cells was evidenced by the activity of cilia when live preparations were viewed under the phase-contrast microscope.

There was no formation of endometrial glands in vitro and therefore such phenomena as luteinizing effects could not be studied. The majority of cells grown appeared to be of the endometrial stroma type.

ALVIN M. SIEGLER

**Frank and Gordon: Reproductive Performance of Women With Pelvic Pain of Long Duration: Some Observations on Associated Psychopathology, p. 440.**

An experimental group of 32 women who complained of chronic intermittent pelvic pain of from 6 months' to many years' duration were studied. Ten cases were diagnosed as the pelvic congestion syndrome. The control group consisted of 25 pregnant women from the prenatal clinic, unselected except in respect to parity, 11 of them primiparas and 14 multiparas.

All patients in the experimental group demonstrated a marked psychiatric disturbance of function, ranging from severe neurotic symptomatology to borderline and overt psychotic manifestations. All complained of frustrating life situations centered upon their marital relationships. They were incapable of mature solutions to marital problems and consequently developed feelings of helpless rage toward their husbands, with tension, and depression. All women with pelvic pain showed severe disturbances in their sexual performance. Menstruation was unacceptable to most of them. Information was known on the pregnancies of 16 of the 24 women who had children. All of these pregnancies were attended by physical symptoms and emotional disturbances.

The incidence of severe psychiatric disorders in the control group was high, about 50 per cent, as compared with 100 per cent in the experimental group. There was an absence of a consistent pattern of disturbance in the control group and only one patient had suffered any acute physical distress during early menses. The emotional disturbances during pregnancy were milder.

On one of the psychological tests, i.e., figure drawings, the experimental group reflected an unusually infantile level of personality integration and functioning. There was also a denial of sexual differences.

ALVIN M. SIEGLER

**Tompkins: Preservation of Fertility by Conservative Surgery for Ectopic Pregnancy, p. 448.**

Salvage of the oviduct is easily accomplished in some cases of ectopic tubal pregnancy. A plea is made for conservative surgery and preservation of the uterine tube.

After controlling the hemorrhage, the operator proceeds to manage the tubal pregnancy in the gentlest way. If implantation is in the distal half of the tube, the oviduct is opened with scissors and the conceptus is scooped out. If implantation is in the proximal half of the tube, the mass should be incised and the conceptus enucleated. Bleeding from the incision is not difficult to control. Two points deserve the strongest emphasis: (1) Absolutely no attempt should be made to close the incised tube. (2) Free blood in the peritoneal cavity should not be evacuated. In essence, the procedure is to slit the tube, enucleate the conceptus, stop the bleeding, and leave the uterine tube open.

The above procedure was followed in 12 tubal pregnancies and in each of these the convalescence was uneventful. Six of the patients had infertility problems, one subsequently developed an intrauterine pregnancy, and 2 contralateral tubal pregnancies. One patient had an intrauterine pregnancy following bilateral ectopic pregnancies. Three patients had salpingograms; the uterine tube which had been operated upon was roentgenographically normal. Secondary laparotomies were performed on 3 patients and the oviduct from which an ectopic pregnancy had previously been removed appeared to be normal.

ALVIN M. SIEGLER

*Vol. 7, November-December, 1956.*

\*Greenblatt, R. B., Vazquez, E., and McLendon, I. C.: Endocrinopathies and Infertility: 1. Acromegaly and Pregnancy, p. 498.

\*Shettles, Landrum B.: The Ovum in Infertility, Abortion, and Developmental Anomaly, p. 561.

**Greenblatt, Vazquez, and McLendon: Endocrinopathies and Infertility: 1. Acromegaly and Pregnancy, p. 498.**

The authors report the thirty-sixth case of pregnancy associated with acromegaly. A 28-year-old woman was referred because of infertility and functional amenorrhea. Roentgenographic studies showed an irregularly enlarged sella turcica with thinning of the dorsum sellae. There was no tufting of the terminal phalanges. Hormone assays and chemical studies supported the presumptive diagnosis.

Radiation therapy of the pituitary was avoided in order to learn the effect of hormone treatment alone. Estrogens were administered cyclically and withdrawal periods occurred at monthly intervals. Physical appearance, symptomatology, and psychological status were remarkably improved. Following the implantation of pellets of progesterone, ovulatory menses occurred. Two years and four months after the inception of treatment, the patient became pregnant. Ten months after delivery of the first child she successfully conceived and was delivered of another normal infant. Despite clinical improvement, the pituitary continued to enlarge and some tufting of the terminal phalanges appeared.

ALVIN M. SIEGLER

**Shettles: The Ovum in Infertility, Abortion, and Developmental Anomaly, p. 561.**

This is an excellent review of the current literature on the role of the ovum in infertility, spontaneous abortion, and anomaly of the conceptus. It shows unequivocally the importance of a good ovum for normal conception and subsequent development.

The formation of normal ova is closely associated with the age of the individual. When all factors are considered, the prime years for bearing offspring are between 20 and 30. After 35 the hazards to the embryo are markedly increased; however, the risks need not outweigh the desire for offspring. In human reproduction the over-all natural tendency to eliminate the unfit is a fortunate phenomenon. Patients can be informed of these considerations, and yet, for the most part, they are willing to accept the conditions.

ALVIN M. SIEGLER

### **The Journal of Clinical Endocrinology and Metabolism**

*Vol. 16, November, 1956.*

\*Dowling, J. T., Freinkel, N., and Ingbar, S. H.: Effect of Diethylstilbestrol on Binding of Thyroxine in Serum, p. 1491.

**Dowling, Freinkel, and Ingbar: Effect of Diethylstilbestrol on Binding of Thyroxine in Serum, p. 1491.**

During pregnancy there is thyroid hyperplasia accompanied by an increased concentration of circulating thyroid hormone and increased uptake of radioiodine. These

changes, ordinarily associated with the thyrotoxic state, during pregnancy are not accompanied by symptomatic stigmas of thyrotoxicity nor by an increased basal oxygen consumption beyond that which can be attributed to fetal needs. There is a marked increase in the thyroxine-binding capacity of the thyroxine-binding protein (TBP) during pregnancy. Although the origin of this alteration is unknown, changes in the metabolism of estrogens may be contributory.

The authors studied 16 persons with various states of thyroid activity for the thyroxine-binding capacity of TBP after administering large doses of diethylstilbestrol. All patients showed an increased capacity of thyroxine-binding serum proteins. The effect of diethylstilbestrol was not dependent on normal function of the thyropituitary axis. The exact mechanism by which the estrogens produce this effect remains questionable.

J. EDWARD HALL

### Muenchener Medizinische Wochenschrift

*Vol. 98, No. 40, October 5, 1956.*

\*Kremling, H.: On the Possibility of Treating Pruritus Vulvae by Surgery, p. 1367.

**Kremling: On the Possibility of Treating Pruritus Vulvae by Surgery, p. 1367.**

It is suggested that cases of pruritus vulvae which are refractory to other treatment may be cured by surgery. The cases selected should have no underlying pathology such as leukoplakia, diabetes mellitus, or parasitic infestations. The operative procedure consists of undermining the skin edges of the vulva and severing sensory nerve endings in the area. If cases are properly selected, the operation will rarely be done.

WALTER F. TAUBER

*Vol. 98, No. 42, October 19, 1956.*

Brilmayer, H., and Marguth, F.: Hypophysectomy in Patients With Carcinoma, Diabetes Mellitus, or Hypertension, p. 1427.

### Zentralblatt für Gynäkologie

*Vol. 78, No. 32, August 11, 1956.*

\*Mikulicz-Radecki, F.: The Age of Women Undergoing Gynecologic Operations at the Free University of Berlin, p. 1241.

Schmidt-Elmendorff, H. R., and Dibbelt, L.: Cancer Detection Clinics and the Percentage Increase of Early Cases of Carcinoma of the Cervix, p. 1250.

Schmid, H. H.: On the Technique of the Schauta Operation, p. 1254.

Igel, H., and Mueller, W.: Results of Cytologic Examination in Screening for Gynecologic Carcinomas at the Charité (Berlin), p. 1257.

**Mikulicz-Radecki: The Age of Women Undergoing Gynecologic Operations at the Free University of Berlin, p. 1241.**

The operative mortality in 392 major gynecologic operations in women (aged 61 to 85 years) was 7.3 per cent in comparison with 2.2 per cent, the general operative mortality at the Free University of Berlin. Although 80 per cent of the deaths were in the cancer group, there was a high incidence of embolic and other circulatory complications. The conclusion drawn is that indication for surgery in an old patient should be carefully evaluated.

WALTER F. TAUBER

*Vol. 78, No. 34, August 25, 1956.*

Hansen, A.: Prevention of Postoperative Thromboembolic Phenomena in Gynecology With the Use of a Coumarin Derivative, p. 1321.

Szirmai, E.: Phlegmasia Caerulea Dolens and Coagulation Determinations, Antepartal and Puerperal, p. 1327.

\*Koester, H. J.: Ascorbic Acid Requirements Following Gynecologic Operations, p. 1334.

Gitsch, E.: Why Does Pregnancy Affect the Thyroid After Thiouracil? p. 1341.

Kriz, K.: Sheehan's Syndrome With Congenital Hypofibrinogenemia, p. 1347.

**Koester: Ascorbic Acid Requirements Following Gynecologic Operations, p. 1334.**

The author reviews the function of ascorbic acid in the activity of the adrenal cortex, in detoxification, in wound healing and fibrosis, and in hemopoiesis. Following gynecologic operations, 116 patients were treated with ascorbic acid. The postoperative course was much improved, with reduced incidence of infections and hemorrhages, and better emotional outlook. The requirements of ascorbic acid are independent of the extent of surgery, but are related to any pre-existing deficiency. It is suggested that 1 Gm. ascorbic acid be administered daily for 10 days after operation. This treatment reduces and frequently eliminates the stress syndrome described by Selye. ACTH and cortisone are made unnecessary in postoperative care by this regimen, and indeed steroid therapy without vitamin C is useless.

WALTER F. TAUBER

*Vol. 78, No. 36, September 8, 1956.*

\*Thomaschek, G.: Sequellae of Thromboembolic Phenomena, p. 1405.

Raessler, R.: The Problem of Delayed Sequellae of Thrombosis, p. 1416.

Waldeyer, L.: Partial Occlusion of the Introitus Due to Adhesions of the Labia Minora Following Spontaneous Delivery, p. 1421.

Reiffenstuhl, G.: Sarcoma of the Vagina—A Case Report, p. 1424.

**Thomaschek: Sequellae of Thromboembolic Phenomena, p. 1405.**

Successful treatment of thromboembolic phenomena depends upon early recognition at a stage when definite diagnosis is difficult or impossible. In doubtful cases, therapy should be undertaken; thus, postoperative pleuritis or bronchopneumonia should be considered as possibly caused by pulmonary infarcts. However, indiscriminate "routine prophylaxis" with anticoagulants puts an excess load on laboratory facilities and is not completely innocuous. Prophylactic anticoagulant therapy should be limited to patients with previous thromboembolic diseases in whom circulatory disturbances may be anticipated. Such treatment must be supervised by laboratory tests and expert advice. Adequate doses of heparin followed by coumarin derivatives must be used, since lesser amounts can produce the very difficulties which are to be guarded against.

WALTER F. TAUBER

*Vol. 78, No. 37, September 15, 1956.*

Schaumkell, K. W., and Stange, H. H.: Clinical, Psychological, and Histological Examinations of Male Pseudohermaphrodites With Complete Feminization, p. 1449.

Jacobi, H.: Delivery in Extremis and Postmortem Without Cesarean Section, p. 1459.

Vorster, R.: Regulation of Duration and Loss of Blood During Menses With Testosterone, p. 1462.

\*Scholz, H.: The Use of Protamine Sulfate and Toluidine Blue in Uterine Bleeding, p. 1470.

**Scholz: The Use of Protamine Sulfate and Toluidine Blue in Uterine Bleeding, p. 1470.**

Protamine sulfate and toluidine blue were used in 54 cases of dysfunctional bleeding in the absence of pathologic findings on pelvic examination or suspicion of malignancy. Seventy per cent of those treated with protamine sulfate and 82 per cent of the toluidine blue series stopped bleeding. Most of these were cases of menorrhagia. Six of 9 patients with metrorrhagia did not respond and in all these patients cystic glandular hyperplasia was found on curettage.

WALTER F. TAUBER



## Correspondence

### Follow-up Report on Patient With Hyperlipemia of Pregnancy

To the Editors:

In the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 71: 326, 1956, Millen, Russ, Eder, and Barr reported the case of a nondiabetic, previously healthy woman who at the end of her pregnancy developed hyperlipemia and clinical signs of acute pancreatitis. Total lipid of her plasma reached the unprecedented concentration of 20,925 mg. per 100 ml. Some notes concerning her subsequent course may be of interest to your readers.

She had been delivered on May 22, 1953. Following a puerperium stormy because of left lower lobe atelectasis, bilateral thrombophlebitis, and pulmonary infarctions, she returned to her home in apparently good health. Examinations of her plasma on June 5 and Oct. 20, 1953, still showed an abnormal content of neutral fat. On Jan. 21, 1954, the cholesterol content was 295 mg. per 100 ml.

She was seen again about six weeks after another conception, when concentration of her plasma cholesterol was still 296 mg. per 100 ml. On March 28, 1956, during the sixth month of pregnancy, her serum was turbid and cholesterol and phospholipid concentrations had risen, respectively, to 586 and 816 mg. per 100 ml. On May 7, the appearance of her plasma resembled cream; cholesterol and phospholipid concentrations exceeded 1,000 mg. per 100 ml. At this time she was instructed to omit all fat from her diet. This she conscientiously attempted with the result that, at the time of delivery, gross lipemia was no longer apparent. The plasma remained slightly turbid; cholesterol and phospholipid concentrations were reduced, but still highly abnormal. On May 25, she was delivered without symptoms of pancreatitis or other untoward incident of a boy who appeared to be normal in all respects and who did not share the hyperlipemia of his mother. The placenta showed no unusual degree of atherosclerosis.

Because of the improvement in the hyperlipemia state following a fat-free diet, it was thought that her malady could be classified as idiopathic hyperlipemia. Since, in this condition, hyperlipemia following a fat meal clears more slowly than normal and since good results have followed spacing intake of fat, she was encouraged to limit fat ingestion to one meal each day. On this regimen, she did well. On Oct. 4, 1956, her plasma showed no turbidity and the cholesterol concentration was 311 mg. per 100 ml.

Lipid relationships observed over a three year period are indicated in the table.

DATE	CONDITION	CHOLESTEROL (MG./100 ML.)	PHOSPHOLIPIDS (P × 25) (MG./100 ML.)	TOTAL LIPIDS (MG./100 ML.)	NEUTRAL FAT
5/22/53	Ante partum	2,069	2,180	20,925	16,500
	Post partum	2,141			
	Cord blood	64			
5/ 5/53	2 weeks post partum	749		2,340	1,203
10/20/53	5 months post partum	350	333	2,478	1,550
1/20/54		295	320		
11/ 1/55	6 weeks pregnant	296	349	1,216	441
3/28/56	6 months pregnant	586	816	3,496	1,745
5/ 7/56	7½ months pregnant	1,029	1,202	8,215	5,490
5/28/56	At delivery	729	660	2,552	976
	Cord blood	84	113		
5/31/56	4 days post partum	573	536		
10/ 4/56	4½ months post partum	311	327		

ELLA M. RUSS  
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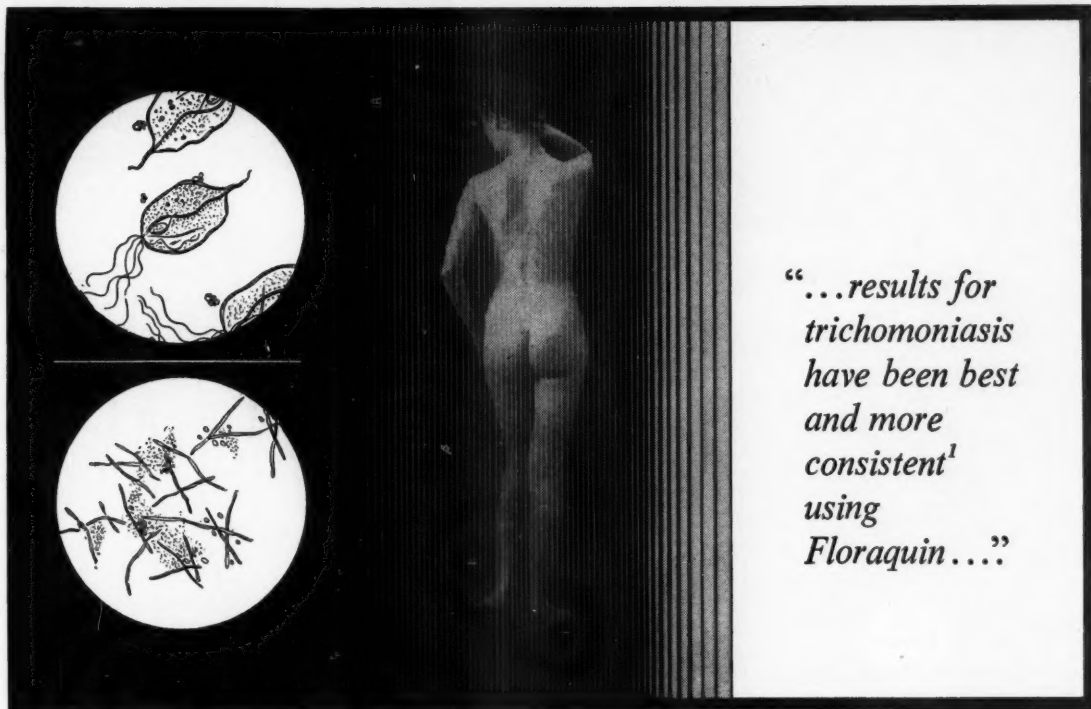
Applications for certification, new and reopened, for the 1958 Part I Examinations are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of applications is Sept. 1, 1957. No applications can be accepted after that date.

Candidates for admission to the Examinations are required to submit with their application a typewritten list of all patients admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for reopening of their application. This information is to be attested to by the Record Librarian of the hospital or hospitals where the patients are admitted and submitted on paper 8½ by 11 inches. Necessary detail to be contained in the list of admissions is outlined in the Bulletin and must be followed closely.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office.

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1. Pitt, M. B.: Leukorrhea. Causes and Management, J. M. A. Alabama 25:182 (Feb.) 1956.
2. Parker, R. T.; Jones, C. P., and Thomas, W. L.: Pruritus Vulvae, North Carolina M. J. 16:570 (Dec.) 1955.

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Cartwright, E. W.: *Dramamine in Nausea and Vomiting of Pregnancy*, *West. J. Surg.* 59:216 (May) 1951.

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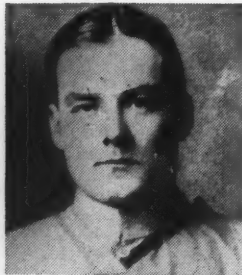
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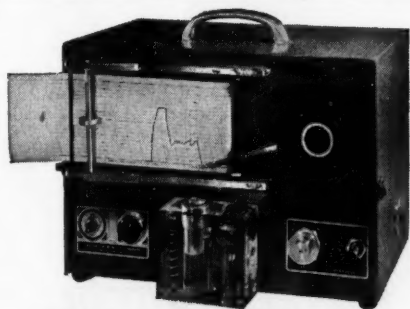
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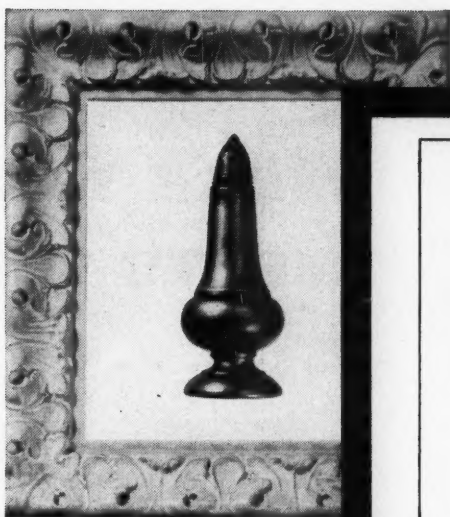


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### **Suppression of Lactation:**

*Actually no breast engorgement, pain or induced vaginal bleeding*<sup>2,3</sup> complicates the postpartum use of Estan in the recommended dosage. Well tolerated Estan is effective in relatively small oral dosage.

### **Recommended dosage:<sup>1</sup>**

Tablets t.i.d. on the first 2 postpartum days,  
Tablets t.i.d. for the following 2 days, and  
Tablet t.i.d. for one day.

**Applied:** In bottles of 30 and 100 scored tablets.

### **Other indications:**

*Relief of disturbing senescent symptoms in both men and women* is readily provided by the combination of estrogen and androgen.<sup>4,5</sup> Additive anabolic effects increase the sense of well-being.

### **Dosages:**

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Osteoporosis and senescence—1 or 2 tablets t.i.d. for 1-2 months, then 1 or 2 tablets per day.

\*Follow 21 days of treatment with 7 to 10 days of rest.

White Laboratories, Inc., Kenilworth, New Jersey

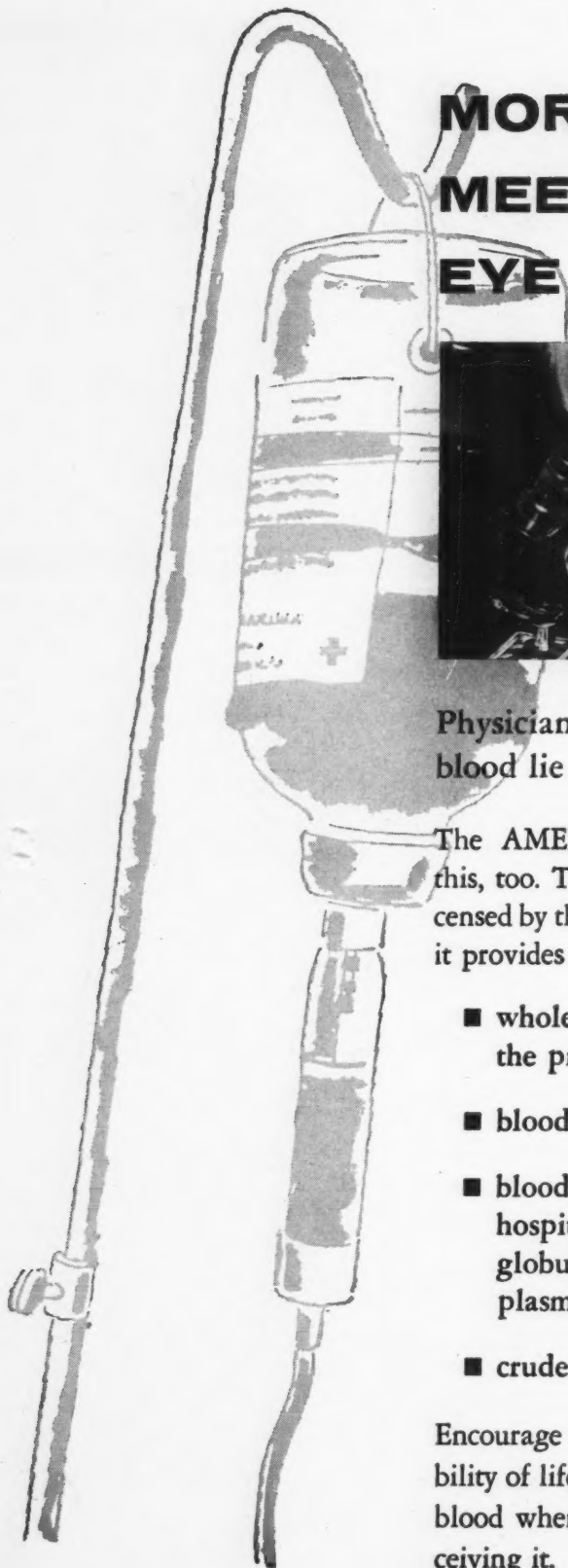
### **References:**

1. L. E., and McCarthy, J. J. Jr., *Pennsylvania M. J.* 59-914, August, 1956.  
2. J., *Obst. & Gynec.*, 7:422, April, 1956.

3. Rienzo, J. S., *Am. J. Obst. & Gynec.*, 66:1248, December, 1953.

4. Masters, W. H., *J. Am. Geriatrics Soc.*, 3:389, June, 1955.

5. Masters, W. H., and Ballew, J. W., *Geriatrics*, 10:1, January, 1955.



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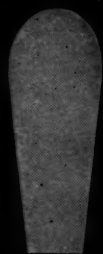
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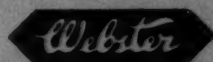
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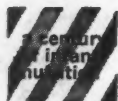
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